Nutrition and Health
Series Editors: Adrianne Bendich · Connie W. Bales

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel *Editors*

Nutrition and Diet in Maternal Diabetes

An Evidence-Based Approach

Humana Press

Nutrition and Health

Adrianne Bendich, Ph.D., FACN, FASN
Connie W. Bales, Ph.D., R.D., Series Editors

The Nutrition and Health series has an overriding mission in providing health professionals with texts that are considered essential since each is edited by the leading researchers in their respective fields. Each volume includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research and (9) balanced, data driven answers to patient/health professionals questions which are based upon the totality of evidence rather than the findings of a single study.

Nutrition and Health is a major resource of relevant, clinically based nutrition volumes for the professional that serve as a reliable source of data-driven reviews and practice guidelines.

More information about this series at http://www.springer.com/series/7659

Rajkumar Rajendram · Victor R. Preedy
Vinood B. Patel
Editors

Nutrition and Diet in Maternal Diabetes

An Evidence-Based Approach

Humana Press

Editors
Rajkumar Rajendram
Department of Nutrition
King's College London
London
UK

Victor R. Preedy
Department of Nutrition
King's College London
London
UK

Vinood B. Patel
Department of Biomedical Sciences
University of Westminster
London
UK

Nutrition and Health
ISBN 978-3-319-56438-8 ISBN 978-3-319-56440-1 (eBook)
https://doi.org/10.1007/978-3-319-56440-1

Library of Congress Control Number: 2017937465

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Diabetes (Type 1, Type 2 or gestational) in pregnancy can have adverse consequences for the fetus and post-natal growth. The effects of maternal diabetes can also persist into adulthood via fetal programming. Breastfeeding may also be problematic. However, these are simple concepts as maternal diabetes can also be considered as a global issue. Worldwide, gestational diabetes occurs once in every twenty-five pregnancies. In the United States the present rate of gestational diabetes lies between 5 and 9%. However, regardless of its aetiology, diagnosis or prevalence, it is important to point out that nutritional and/or dietary factors play an integral part in maternal diabetes. For example good dietary practises and advice are beneficial in maintaining adequate blood glucose control. Poor dietary practises before pregnancy, on the other hand, leads to an increase in body mass index (BMI), which in turn is a risk factor for both Type 2 and gestational diabetes. These interrelationships between diagnosis, causative factors, outcomes, diet and nutrition are complex. They involve molecular biology, cells and organs. Hitherto these associations and links have not been previously formulated into a single scientific treatise. This is however addressed in **Nutrition and Diet in Maternal Diabetes: An Evidence Based Approach**. Coverage including global and country-specific aspects, diagnosis and biomarkers, genetics and gene expression, signalling, neurology, obesity, cardiovascular disease, polycystic ovary syndrome, glucose and insulin metabolism, minerals, vitamins, fatty acids, dietary supplements, exercise and many other areas. Where appropriate, chapters have a section on either ***Recommendations*** or ***Guidelines*** and all contributions have a set of ***Key Points***.

Contributors are authors of international and national standing, leaders in the field and trendsetters. Emerging fields of science and important discoveries are also incorporated in **Nutrition and Diet in Maternal Diabetes: An Evidence Based Approach**.

This book is designed for nutritionists and dietitians, endocrinologists, public health scientists, medical doctors, midwives, obstetricians, paediatricians, epidemiologists, health care professionals of various disciplines and policy makers. It is designed for teachers and lecturers, undergraduates and graduates, researchers and professors.

London, UK

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel

Series Editor Preface

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading and emerging authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"**Nutrition and Diet in Maternal Diabetes**", edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel is a most timely and very welcome addition to the Nutrition and Health Series and fully exemplifies the Series' goals. It is hard to imagine that it is only seven years ago that international criteria were agreed upon concerning the diagnosis of gestational diabetes during the second trimester of pregnancy. Yet, there are many nations that have not adopted these criteria and new research discussed within this volume point to the potential for earlier diagnosis, thus enhancing the potential to identify at risk women earlier and reduce associated adverse effects. This is the first volume to specifically address the nutritional aspects of maternal hyperglycemia from a global perspective. The emphasis is on identifying nutritionally related risk factors for developing gestational diabetes, for reducing the risks of Type 1 diabetes during pregnancy, for managing the nutritional components of gestational diabetes mellitus and other causes of hyperglycemia during pregnancy and postpartum. Chapters identify the key potential adverse effects of hyperglycemia during pregnancy on both the mother and offspring and outline potential nutritional strategies that can be of benefit. As one of the major risk factors for developing gestational diabetes is related to maternal weight and weight gain, it is obvious that nutrition is a key factor in all aspects of gestational diabetes and hyperglycemia in pregnancy, and this is the focus of "Nutrition and Diet in Maternal Diabetes".

The editors of this volume are experts in their respective fields and represent the medical profession as well as the academic research community. Dr. Rajkumar Rajendram is an intensive care physician, anaesthetist and peri-operative physician. He was trained in general medicine and intensive care in Oxford, and he attained membership in the Royal College of Physicians (MRCP) in 2004. Dr. Rajendram then trained in anaesthesia and intensive care in the Central School of Anesthesia, London Deanery and became a Fellow of the Royal College of Anesthetists (FRCA) in 2009. He is one of the first intensivists to become a Fellow of the faculty of intensive care medicine (FFICM). Dr. Rajendram recognized that nutritional support was a fundamental aspect of critical care and, as a visiting research Fellow in the Nutritional Sciences Research Division of King's College London; he has published over 50 textbook chapters, review articles, peer-reviewed papers and abstracts. Professor Victor R. Preedy is a senior member of King's College London where he is Professor of Nutritional Biochemistry. He is also Director of the Genomics Centre and a member of the School of Medicine. He is a member of the Royal College of Pathologists, a Fellow of the Society of Biology, the Royal College of Pathologists, the Royal Society for the Promotion of Health, the Royal Institute of Public Health, the Royal Society for Public Health and in 2012 a Fellow of the Royal Society of Chemistry. Dr. Vinood B. Patel is a Senior Lecturer in Clinical Biochemistry at the University of Westminster and honorary Fellow at King's College London. Dr. Patel obtained his degree in Pharmacology from the University of Portsmouth, his Ph.D. in protein metabolism from King's College London and completed postdoctoral research at Wake Forest University School of Medicine. Dr. Patel is a recognized leader in alcohol research and was involved in several NIH funded biomedical grants related to alcoholic liver disease. Dr. Patel has edited biomedical books in the area of nutrition and health and disease prevention and has published over 160 articles.

The 37 chapters within this clinically important, practice-oriented volume provide the reader with a comprehensive examination of the growing global prevalence and consequences of both the effects of pre-existing diabetes as well as pregnancy-induced gestational diabetes mellitus (GDM) on maternal as well as fetal health. Data consistently show that GDM is associated with complications such as increased birth weight, macrosomia, caesarean birth and preterm birth. Women who are diagnosed with GDM have a significantly increased risk of developing Type 2 diabetes within 10 years. GDM also increases the risk of preeclampsia.

Genetic factors that affect insulin resistance, metabolomics, oxidative stress and other critical risk factors are reviewed in separate chapters. There is a broad-based review of the current definitions of gestational diabetes as well as an in-depth discussion on diagnosis and maternal co-morbidities, neonatal effects and postpartum maternal effects of gestational diabetes.

This comprehensive volume is organized into nine parts that include chapters on the clinical basis of gestational diabetes; pregnancy in women with Type 1 diabetes; relevant research from several different geographic areas; genetic factors associated with gestational diabetes and its consequences; effects of pre-existing conditions, such as bariatric surgery, on maternal health when gestational diabetes is also a critical factor; reviews of clinical data from dietary intervention studies; postpartum effects of gestational diabetes; breast feeding; dietary components and weight gain effects, and finally, a chapter devoted to providing additional resources and references on this expanding field of obstetrics.

Part I. Definitions, Characterization and Diagnosis

Part I begins with an historic overview of the evolution of the terminology used to describe maternal diabetes and Chap. 1 reviews in detail the development of diagnostic criteria for maternal gestational diabetes beginning with the criteria provided by O' Sullivan et al. in 1964 based on an oral glucose tolerance test (OGTT) at 22 weeks gestation. During the 1980s there was an attempt to use the same

criteria for Type 2 diabetes diagnosis for gestational diabetes. However, the growing knowledge of the adverse effects of higher than normal circulating glucose levels on the fetus resulted in the impetus to develop globally acceptable criteria for diagnosis. In 1980, the World Health Organization (WHO) made the recommendation to use the OGTT diagnostic criteria used to diagnose Type 2 diabetes and impaired glucose tolerance. Unfortunately, different National associations chose different blood glucose thresholds to detect abnormalities in pregnancy. The result was a variety of studies reporting different estimates and confusion for clinicians on how to define the condition.

As more women of reproductive age started to develop Type 2 diabetes, it was important to distinguish between pre-existing but undiagnosed diabetes in pregnancy from the milder form (GDM) that develops at 22 weeks and resolves postpartum. For many years, sets of risk factors were used to screen for the potential to develop gestational diabetes and it was not until 2008 that the results of the Hyperglycemia and Adverse Pregnancy Outcomes study were published and helped to clarify the serious adverse effects of high maternal glucose levels on the fetus and neonate. This landmark study enrolled over 25,000 pregnant women in an international multi-centre study and followed them through pregnancy. The results led to recommended diagnostic criteria for GDM representing the average glucose values at which the odds for birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percentage body fat >90th percentile reached 1.75 times the odds of these outcomes. The thresholds established by this study were adopted by many National and Medical Society guidelines and were also recommended by the American Diabetes Association in its 2011 position statement. We learn that in 2013 the World Health Organization proposed new criteria for the diagnosis and definition of hyperglycemia first detected in pregnancy. The definition distinguishes the more serious diabetes in pregnancy (DIP), which is more likely to persist beyond the birth and can cause serious fetal abnormalities early in pregnancy, from the relatively milder gestational diabetes. The new definition calls for an understanding of the burden of hyperglycemia in pregnancy and its relationship with the growing epidemic of Type 2 diabetes and distinguishes DIP from GDM based on the degree of hyperglycemia; a reflection that the risk of serious complications is much higher in diabetes in pregnancy than in GDM. Where studies previously reported the prevalence of GDM, under the new definition, these figures would also include the more severe hyperglycemia classified as diabetes in pregnancy under the broad title of hyperglycemia first detected in pregnancy (HFDP). Added to this definition are women with diagnosed diabetes who become pregnant; the term hyperglycemia in pregnancy (HIP) encompasses the burden of any glucose intolerance in pregnancy.

The chapter also cites the most current data on prevalence: The International Diabetes Federation (IDF) estimates that in 2015, 16.2% of live births to women between the ages of 20 and 49 years had some form of hyperglycemia in pregnancy. The vast majority of those cases were due to the milder form of gestational diabetes (85.1%) while the rest represent pre-existing diabetes only about half of which was diagnosed prior to pregnancy. This figure translates to at least 20.9 million live births affected by some form of HIP. This informative chapter also includes 8 relevant tables and figures.

The third chapter examines the potential of various diagnostic markers to identify hyperglycemia in pregnancy at the earliest time possible as the adverse consequences to maternal and fetal health are cumulative. The authors suggest that biomarkers, including the glycation of proteins such as albumin and fructosamine, represent glycemic control for the preceding 2–3 weeks be considered, as this would serve as an earlier indicator of glycemic control in a dynamic condition, such as pregnancy. These indicators are not dependent on the half-life of erythrocytes as is seen with haemoglobin A1C. It is important to have relevant choices for following pregnant women's glucose control especially if they are diagnosed with GDM.

The last chapter in this part, Chap. 4, reviews the authors' data concerning an Australian study that found an increased risk of GDM in pregnant women who showed signs of depression earlier during their pregnancy. The study followed over 3000 pregnant women and found a significant association between having an Edinburgh Perinatal Depression Scale > 13 at the first visit to pregnancy care (12–17 weeks) and the diagnosis of GDM at around 28 weeks of pregnancy even when the data were

adjusted for parity, smoking, maternal weight, age and ethnicity. As a similar association has been found in women with Type 2 diabetes, and the risk of developing Type 2 diabetes is significantly increased in women who developed GDM, greater awareness of the potential development of depression during pregnancy and afterwards in women with GDM is warranted.

Part II. The Type 1 Diabetic Mother

Chapters 5 and 6 examine the effects of Type 1 diabetes during pregnancy and the factors that further exacerbate the potential for adverse effects to both the pregnant woman and her fetus/neonate. Chapter 5 reviews the authors' findings concerning the increased, synergistic risk of adverse pregnancy outcomes associated with having Type 1 diabetes and being either overweight or obese. Their data from Sweden, which has a high rate of Type 1 diabetes that is increasing over time, indicate that compared to normal weight women with Type 1 diabetes the overweight group had a 77% higher risk for major fetal malformations, a 25% increased risk for premature delivery and a 70% increased risk of caesarean section. Chapter 6 describes the importance of frequent monitoring of glucose control during pregnancy in the Type 1 diabetic females. Hyperglycemia is detrimental to the fetus. A fivefold increase in the rate of cardiovascular malformations and a more than twofold increase in the rate of neural tube defects and urinary malformations have been documented and thus the chapter provides important practice-oriented advice to healthcare providers to emphasize the critical need for planned pregnancy and tight glucose control especially during the weeks of embryogenesis and fetal growth.

Part III. Global Findings in Gestational Diabetes

The next three chapters report on the prevalence and care of pregnant women who develop GDM in Iran, China or Italy. As we learned above, there can be wide differences in the prevalence of pregnancy-related complications and GDM rates are increasing globally. Chapter 7 provides important data on the prevalence of GDM: In Iran, there is a 4.9% estimated prevalence of GDM which varies greatly between different regions, from 0.7% in the west to 18.6% in the south near Tehran. Overweight, obesity, maternal age and lack of exercise are some of the major risk factors identified. WHO guidelines for identifying women with GDM are followed and once identified, measures to control serum glucose levels are undertaken and outlined in the chapter. The chapter concerning GDM in China, Chap. 8, highlights the data related to vitamin D status. In China, mean levels of circulating vitamin D among pregnant women were relatively low and about 60% are considered deficient. The potential causes are outlined and include Asian skin tint, older age of pregnant women, increased rate of overweight and obesity. Recent Chinese data showed that pregnant women with vitamin D deficiency at the 16th–20th gestational week had a higher prevalence of gestational diabetes and preterm delivery than those with sufficient vitamin D. This is a relatively new area of research and there are few intervention data to help healthcare providers to determine whether to either provide vitamin D supplementation or at what level of supplementation. Chapter 9 looks at the current diagnosis and screening criteria used in Italy and the chapter provides recommendations for increasing the sensitivity of screening tools. We learn that GDM occurs in about 11% of the Italian population and it is also associated with an increased rate of maternal and fetal complications compared with normal pregnancy. Maternal complications that occur with an increased frequency include: preterm delivery, polyhydramnios, macrosomia, shoulder dystocia, stillbirth and operative delivery. Fetal complications associated with an increased risk include: neonatal hypoglycemia,

jaundice, polycythemia, hypocalcemia and increased frequency of neonatal intensive care unit admission. Development of data that can identify risk factors early in pregnancy that do not depend on prior pregnancy results was a strong driver for this research team. They found that the most important variable for differentiating the risk of GDM was fasting plasma glucose (FPG). Women with a FPG value lower than 4.4 mmol/l had the lowest GDM prevalence. Patients with a FPG value higher than 5.1 mmol/l represented the subgroup of women with the highest prevalence of GDM (OR 26.5; 95% CI 14.3–49.0). In women with FPG values between 4.5 and 5.1 mmol/l, the risk of GDM was further differentiated on the basis of pre-pregnancy BMI values. Women with a pre-pregnancy BMI in the overweight range or above had a higher risk of developing GDM (OR 7.0; 95% CI 3.9–12.8) that was almost double compared with women with a normal pre-pregnancy BMI (OR 3.7; 95% CI 2.1–6.7). These data were used in Italy to derive screening criteria and the implementation is described in detail.

Part IV. Genetic and Molecular Factors Associated with Maternal Gestational Diabetes

Five chapters review the current associations between GDM and genetic as well as epigenetic findings. The first three chapters describe potential early markers of GDM that are related to maternal genetic alterations. Chapter 10 describes the epigenetic alterations in biomarkers that are associated with GDM. The chapter reviews the disease-specific metabolic imbalances indicative of low-grade inflammation and increased oxidative stress that can adversely affect the health of both the fetus and pregnant woman. Using metabolomics strategies, the authors have verified that alterations in both the level and composition of plasma lysophospholipids are the most prominent changes that correlate with the glycemic state of GDM pregnant women. Using these techniques, they hope to be able to identify GDM earlier and reduce the adverse metabolic consequences. The authors of Chap. 11 look at the data concerning a bioactive molecule, adiponectin, produced by adipose tissue that is one of the factors involved in regulating glucose metabolism. During pregnancy, the serum levels of adiponectin change to meet the needs of the growing fetus. Abnormally low levels of adiponectin have been associated with GDM that is associated with a glucose intolerance state. The authors suggest that serum adiponectin concentrations may be used as an early marker of GDM risk. Moreover, there are certain alterations in the genes affecting adiponectin synthesis that appear to increase the risk of developing insulin resistance during gestation. Chapter 12 examines the preliminary data associating single nucleotide polymorphisms in the genes encoding retinol binding protein 4 and increased risk of insulin resistance in women with GDM. As this protein is the primary carrier of the essential vitamin, vitamin A, which is critical for normal human reproduction, there appear to be several mechanisms to link genetic alterations in this carrier protein with potential adverse pregnancy outcomes. Further research is recommended by all three chapter authors.

Chapters 13 and 14 examine the increased risks associated with GDM to the mother and offspring. In women who have had GDM, the risk for developing Type 2 diabetes is increased by 7.4 fold compared to women with pregnancies unaffected by GDM. The increased risk appears to be independent of the number of pregnancies affected by GDM. With regard to increased risk of cardiovascular disease, women with GDM who had higher serum glucose when challenged either during pregnancy or postpartum demonstrated increased risk of cardiovascular disease, indicating that peak glucose levels are important predictors for future cardiovascular disease. Chapter 13 also reviews studies that have shown that women with GDM had decreased cardiac output, decreased stroke volume and increased peripheral vascular resistance postpartum, predisposing these women to cardiovascular disease. The final chapter in this part, Chap. 14, reviews data from laboratory animal studies of epigenetic alterations in the hearts of mice born to mothers with the metabolic symptoms of

human GDM. Provision of long chain polyunsaturated fatty acids to maternal diets reduced the risk of developing the cardiac abnormalities. The genetic and molecular mechanisms identified in these studies are illustrated in the seven important figures and table included in this chapter.

Part V. Pre-existing Conditions and Gestational Diabetes Risk

The three chapters in this part examine the additional burdens that are frequently seen in women who develop GDM including hypertension that can be independent of GDM or occur prior to development of GDM; polycystic ovarian syndrome, and obesity that has led to bariatric surgery. Hypertensive disorders of pregnancy (HDP), which also includes the diagnosis of preeclampsia, are often seen in women with GDM, but not always. HDP affects 5–7% of all pregnancies and 10–28% of those with GDM. Chapter 15 examines the major modifiable risk factors for HDP and GDM including glycemic control, obesity and gestational weight gain. This practice-oriented chapter's figure and tables include important recommendations for reducing the risk of HDP prior to pregnancy as well as postpartum recommendations for reduction in risk of maternal cardiovascular disease especially if the pregnancy is affected by preeclampsia.

Although polycystic ovarian syndrome (PCOS) and GDM are distinct conditions, there is a significantly increased risk of GDM in women with PCOS who become pregnant. Chapter 16 reviews the data from several studies that have found that GDM is the most predominant complication during the pregnancy in women with PCOS and the risk of GDM was found to be approximately threefold higher in women with PCOS compared to controls in the most recent study. There are also data that the prevalence of polycystic ovarian morphology is higher in women with a history of GDM. The common denominator of both is insulin resistance which is the main endocrine disruption in PCOS. The chapter includes over 100 relevant references, tables and figures.

Chapter 17 examines the plusses and minuses of bariatric surgery for obese women prior to pregnancy. Bariatric surgery has been shown to be the most effective and durable treatment for obesity and to reduce obesity-related complications during pregnancy. The chapter provides descriptions of the types of bariatric surgeries and reviews the studies that indicate that GDM was reduced in women who had the surgery and lost significant weight prior to becoming pregnant. In addition to lower risk of GDM, there were also decreases in HDP and preeclampsia that were correlated with weight loss rather than the surgery; some of the studies examined women who had pregnancies before and after bariatric surgery. This comprehensive chapter also reviews the potential adverse effects of bariatric surgery on mother and fetus/neonate and provides the reader with over 120 relevant references, tables and figures.

Part VI. Dietary Interventions and Exercise

As discussed above, there is intense research underway to identify new diagnostic tools, many of which include biomarkers related to nutrients. In addition to this research focus, there are six chapters that report on potential interventions to reduce the risk of GDM. Chapter 18 looks at the potential for a supplement of myo-inositol, a stereo-isomeric form of inositol, to reduce the risk of GDM development. Myo-inositol is physically linked to phospholipids in the membranes of all living cells. It is synthesized in the body from D-glucose and is found in various food sources. It affects insulin balance and the chapter reviews the experimental and clinical data that suggest the potential for its supplementation to reduce the occurrence of GDM. The preliminary data appear promising and further large-scale studies are needed.

The next two chapters examine the potential for low-glycemic index (GI) diets and low carbohydrate diets to reduce several of the insulin-resistant adverse effects associated with GDM. Chapter 19 reviews the data linking low-GI and low glycemic load diets with improvement in the management of body weight, glycemia and cardiovascular risks, especially in hyperinsulinemic and insulin-resistant populations. The authors assess the evidence for the treatment of GDM—a condition closely associated with hyperinsulinemia and insulin resistance—with low-glycemic diets. Both this chapter and Chap. 20 review all of the clinical studies available and acknowledge that further research is warranted to determine the optimal protocol for reducing glycemic load during pregnancies affected by GDM.

As discussed above in Chap. 10 that describes the use of metabolomics in the development of diagnostics for GDM, Chap. 21 suggests the individual evaluation of personal food metabolomics may become an important tool in the development of diet strategies. The chapter explains the processes of analysis of the food metabolome (the sum of the detectable metabolites found in the human system as a result of the ingestion and digestion of food components) for identifying dietary biomarkers of GDM, as well as elucidating the mechanisms underlying the relationship between maternal diet and GDM. There is a detailed discussion of the analytical considerations, and sampling methodology required to reproducibly analyze the food metabolome for linking the maternal diet with GDM including the analysis of blood, urine, amniotic fluid, saliva, hair, and breath. The economic considerations are also included in this topic for future research.

Chapter 22 reviews the preliminary data from survey and randomized controlled studies that have examined the potential for microbiome manipulation to prevent and/or treat GDM. There is currently little information on the microbiome composition in pregnant women who develop GDM. However, there is one study that has examined the microbiota composition in insulin-resistant women with previous GDM compared to women who had a normoglycemic pregnancy and found alterations that may affect insulin control. The chapter provides data on probiotic supplements used in studies as well as sources of prebiotics that would help to maintain beneficial probiotic bacterial populations.

The final chapter in this part, Chap. 23, examines the value of exercise for pregnant women who have GDM. The chapter discusses the studies that found that exercise can be of benefit in women with GDM and may be of help in its prevention, although further study is needed. Studies where maternal exercise appears to play an important role in the management of pregnancies complicated by GDM are tabulated. In particular, exercise has been shown to assist with maintaining blood glucose concentrations within the appropriate range. This blood glucose lowering effect of exercise in women with GDM has been demonstrated both acutely and in response to regular exercise participation.

Part VII. Postpartum Effects of Gestational Diabetes

Three chapters examine the postpartum effects of GDM on the mother that are independent of breastfeeding as this topic is discussed separately below. The fourth chapter in this part looks at one critical aspect of the neonate—neurodevelopment. Chapters 24 and 25 concern two related increased risks to women who have GDM. Clinical and epidemiological studies indicate that women who experience GDM while pregnant have a significantly increased risk of glucose intolerance, either in the form of prediabetes or overt Type 2 diabetes that may be measurable in the early postpartum period and also have up to a 60% lifetime risk for developing Type 2 diabetes. The chapter reviews many factors that are associated with the increased risk of postpartum glucose intolerance including: advanced maternal age at pregnancy, a family history of Type 2 diabetes, high pre-pregnancy weight and high pregnancy weight gain, prior GDM and insulin use during pregnancy. Control of excessive weight prior to pregnancy and excessive weight gain during pregnancy are key factors in predicting GDM as well as postpartum hyperglycemia. Two important clinical studies are reviewed: in one

cohort study of 1263 GDM-affected women, pre-pregnancy obesity and excessive pregnancy weight gain were associated with the increased risk of prediabetes or Type 2 diabetes one to five years postpartum. A randomized controlled trial from Spain (The St. Carlos Gestational study) confirmed that a high pre-pregnancy BMI and excess weight gain in early pregnancy are the major potentially modifiable risk factors for GDM. Chapter 26 reviews the mechanisms that may be responsible for the increased risk of cardiovascular disease in women who have had GDM in the past. We learn that women with GDM are at risk of developing sub-clinical inflammation as a component of GDM and the metabolic syndrome (MetS) that may be present postpartum. The chapter identifies emerging biomarkers of MetS including leptin, adiponectin, C-reactive protein, tumour necrosis factor alpha, interleukin 6, plasminogen activator inhibitor 1, fibrinogen and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and cellular molecule (E-selectin). Future research is required to better understand the potential effects of GDM on risk factors for cardiovascular disease in women who have had GDM.

The last chapter in this part, Chap. 27, examines the preliminary data concerning the effects of GDM on the cognitive functions of offspring. In addition to GDM, there are a number of factors, such as obesity, social issues and environment that can affect neurodevelopmental and cognitive outcomes following GDM. The chapter reviews the studies describing the school age follow up of children born to mothers affected with GDM and show a pattern of lower cognitive scores, attention issues, hyperactivity and poor fine motor skills following maternal GDM. Additionally, data linkage studies reinforce concerns regarding neurodevelopmental outcome following maternal GDM and also report a link to autism spectrum disorders. Some studies report adverse neurodevelopmental outcomes following different pharmacological treatment regimens for GDM. Further research studies are proposed by the authors.

Part VIII. Breastfeeding and Maternal Hyperglycemia

The first two chapters in this part examine the effects of GDM on the ability to breastfeed and the effects on breast milk composition. Chapter 28 provides an in-depth insight into the important, long-standing assistance given to both parents in Thailand that promotes exclusive breastfeeding of the neonate for the first 4–6 months of life. Nevertheless, Thai women with GDM suffer a number of physiological changes that often result in problems with breastfeeding. The chapter outlines the three phases of lactogenesis: phase I occurs during 10–22 weeks gestation. Phase II lactogenesis develops after giving birth and 3 days postpartum. Phase III lactogenesis begins after the third day postpartum. Maternal health associated with diabetes, obesity, insulin resistance and nutrition status has effects on all phases of lactogenesis, however, phase II involves the production of prolactin and oxytocin that control early milk production and secretion. GDM is associated with delayed lactogenesis that is linked to insulin resistance and hypothyroid function that decreases production of prolactin and oxytocin. These factors often result in obese women experience breastfeeding problems due to insufficient milk supply. In addition, one-third of postpartum women with GDM reported delayed milk production by the third day postpartum. Other critical issues involve the type of delivery, size and age of the infant at birth, potential hypoglycemia of the infant and maternal hyperglycemia.

Chapter 29 details the peptides found in human breast milk, their functions and the potential effects of GDM on maternal synthesis of these peptides as well as the effects on the infant exposed to breast milk from mothers affected by GDM. The peptides normally found in breast milk are important for the regulation of neonatal metabolic pathways, modulation of appetite, regulation of fluid intake, contribution to bone formation, nutrition, regulation of sleep, blood pressure, intestinal motility, neuropsychiatric events, fat metabolism, stimulation of learning and antimicrobial activities. The

functions of the major peptides are reviewed and the importance of determining the effects of GDM on the concentrations of these bioactive peptides is emphasized.

As discussed above, pregnant women who have Type 1 diabetes are at increased risk of adverse pregnancy outcomes associated with hyperglycemia. Chapter 30 addresses the needs of these women from preconception to postpartum breastfeeding. The chapter reviews the data linking long-term breastfeeding with prevention of future obesity and may protect against development of Type 1 diabetes and Type 2 diabetes in the offspring. Early breastfeeding initiated in the first 30 min of life and repeated 10–12 times/24 h may reduce the risk of neonatal hypoglycemia. In women with Type 1 diabetes, previous experience with breastfeeding, higher educational level and number of feedings in the first 24 h after delivery are positively associated with longer breastfeeding whereas higher pre-pregnancy BMI and smoking are negatively associated with breastfeeding in this population.

Part IX. Specific Dietary Components and Weight Gain

The first three chapters of this six chapter part describe risks of weight gain and the many benefits of controlling total intake as well as intake of carbohydrates pre-pregnancy in women at risk for GDM and during any pregnancy that is affected by GDM. Chapter 31 describes the adverse effects associated with excessive gestational weight gain. Currently, over 50% of women with diabetes gain excessive weight during pregnancy and interventions to modify gestational weight gain have had minimal effect on pregnancy outcomes. Women whose weight gain during pregnancy is outside the recommended ranges are at increased risk of adverse maternal and neonatal outcomes including the development of hypertensive disorders of pregnancy, increased risk of caesarean delivery, increased infant birth weight and postpartum weight retention. Moreover, the attributable risk for childhood obesity was 16.4% for mothers who had excessive gestational weight gain. The chapter reviews the studies that looked at pregnant women with GDM who gained excessive weight during pregnancy and were found to be three times more likely to have a macrosomic infant and other adverse effects. Chapters 32 and 33 review the value of healthful diet choices for the women with GDM and emphasize carbohydrates. Chapter 32 describes the importance of medical nutrition therapy (MNT). Even though there are few available randomized controlled trials investigating the use of MNT in the treatment of GDM, these studies show beneficial effects of MNT for the mother and offspring, including improved glycemic control, appropriate gestational weight gain, lower frequency of insulin therapy and fewer perinatal complications including neonatal hypoglycemia. The chapter reviews the literature and provides valuable tables on the types of foods and intake levels of carbohydrate-containing foods that are associated with fewer adverse effects of GDM. Chapter 33 also provides important tables and references that contain more details about the types of carbohydrates that can benefit women with GDM. The literature review of evidence from randomized trials in GDM suggest that a balanced intake of higher quality complex carbohydrates results in good glycemic control, improved insulin action and improved maternal glucose tolerance, improved lipemia, and vascular benefits, while low-GI diets in particular may reduce the need for insulin, and lower postprandial glycemia. Diets for GDM that can alter maternal/fetal metabolism in late pregnancy are examined, as this is the time when fetal growth accelerates.

The final three chapters in this part examine essential nutrients including fatty acids, folic acid and iron. Chapter 34 looks at the potential for reduced transfer of long chain polyunsaturated fatty acids (LC-PUFAs) from the placenta of the woman with GDM to the fetus and consequent potential for adverse effects on the neurological development of the fetus and neonate. GDM appears to be associated with a significant decrease in the placental transport of LC-PUFAs. The chapter synthesizes the literature that documents the crucial role of LC-PUFAs in the development of the visual and cognitive function in the fetus, and the effects of the decrease in placental transfer of LC-PUFAs. The

accompanying figures help the reader to understand the potential for LC-PUFA deficiency to result in the neurodevelopmental deficiencies associated with infants born to women with GDM. Folate, an essential water-soluble vitamin, also affects fetal neurodevelopment, as shown definitively in women with folate deficiency whose infants develop neural tube birth defects. Chapter 35 examines the interactions between maternal folate status, GDM and effects on the fetus. The author suggests that further research is warranted that examines maternal vitamin B12 status, folate intake levels and birth outcomes especially in women with GDM. This chapter, as with other forward thinking text, provides the foundation for further hypothesis testing. Iron status in the pregnant woman with GDM is the topic of Chap. 36. Iron status is often below recommended levels in women who become pregnant. Iron stores (as reflected in serum ferritin levels) during pregnancy are essential in preventing negative outcomes for both infants and mothers however, there is some evidence that iron supplementation above recommended intake levels may increase the risk of GDM. The chapter reviews the data showing a positive link between a high serum ferritin levels early in pregnancy and the risk of GDM. Increased ferritin levels may be considered as a risk factor for GDM, and may be useful for screening populations at high-risk of GDM.

Part X. Resources

The final chapter in this comprehensive volume, Chap. 37, contains a compilation of important resources for health professionals who are interested in learning more about GDM and the nutritional aspects and consequences of this health condition. The chapter includes lists of relevant journals, books and references as well as websites of interest.

Conclusions

The above descriptions of the 37 chapters attest to the depth of information provided by the 100 + well-recognized and respected editors and chapter authors who come from more than 25 countries around the world and provide a unique perspective on the diagnosis, maintenance and nutritional components that are most relevant to the prevention and treatment of GDM. Each chapter includes fully defined abbreviations for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include over 150 detailed tables and informative figures, an extensive, detailed index and more than 2000 up-to-date references that provide the reader with excellent sources of worthwhile information. Moreover, the final chapter contains a comprehensive list of web-based resources that will be of great value to the health provider as well as graduate and medical students.

In conclusion, “Nutrition and Diet in Maternal Diabetes”, edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel provides health professionals in many areas of research and practice with the most up-to-date, well referenced volume on the importance of maintaining glucose control before, during and after pregnancy so that both mother and child increase their opportunities for enhancing their overall health. The volume serves the reader as the benchmark in this complex area of interrelationships between maternal hyperglycemia, GDM, Type 1 diabetes and genetic as well as epigenetic factors that increase their risk; overweight and obesity prior to pregnancy and during pregnancy especially if it is affected by GDM; the potential adverse pregnancy outcomes to mother, fetus and neonate as well as potential effects on childhood cognition and increased maternal risk of subsequent Type 2 diabetes and cardiovascular disease. Additionally, we learn that GDM reduces the potential for breast feeding and this can greatly impact the health of the infant as well as

the mother. The importance of diet quality including types and quantity of carbohydrates, glycemic index and glycemic load, dietary protein intakes and long chain fatty acids are reviewed in depth. The open questions concerning the diagnosis of GDM are clearly delineated so that students as well as practitioners can better understand the complexities of these issues as well as learn about the newest research in developing more sensitive and earlier diagnostic tools. The editors are applauded for their efforts to develop the first and most authoritative and unique resource in the area of hyperglycemia during pregnancy and its effects on the health of the mother and her child as well as the potential to reduce the risk of diseases associated with GDM, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN, FASN
Series Editor

About the Series Editor

Dr. Adrianne Bendich, Ph.D., FASN, FACN has served as the "Nutrition and Health" Series Editor for more than 20 years and has provided leadership and guidance to more than 200 editors that have developed the 80+ well respected and highly recommended volumes in the Series.

In addition to "**Nutrition and Diet in Maternal Diabetes**", edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel, major new editions published in 2012–2017 include:

1. **Nitrite and Nitrate in Human Health and Disease, Second Edition**, edited by Nathan S. Bryan and Joseph Loscalzo, 2017
2. **Nutrition in Lifestyle Medicine**, edited by James M. Rippe, 2017
3. **Nutrition Guide for Physicians and Related Healthcare Professionals 2nd Edition** edited by Norman J. Temple, Ted Wilson and George A. Bray, 2016
4. **Clinical Aspects of Natural and Added Phosphorus in Foods**, edited by Orlando M. Gutiérrez, Kamyar Kalantar-Zadeh and Rajnish Mehrotra, 2016
5. **L-Arginine in Clinical Nutrition**, edited by Vinood B. Patel, Victor R. Preedy, and Rajkumar Rajendram, 2016
6. **Mediterranean Diet: Impact on Health and Disease** edited by Donato F. Romagnolo, Ph.D. and Ornella Selmin, Ph.D., 2016
7. **Nutrition Support for the Critically Ill** edited by David S. Seres, M.D. and Charles W. Van Way, III, M.D., 2016
8. **Nutrition in Cystic Fibrosis: A Guide for Clinicians**, edited by Elizabeth H. Yen, M.D. and Amanda R. Leonard, MPH, RD, CDE, 2016
9. **Preventive Nutrition: The Comprehensive Guide For Health Professionals, Fifth Edition**, edited by Adrianne Bendich, Ph.D. and Richard J. Deckelbaum, M.D., 2016
10. **Glutamine in Clinical Nutrition**, edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
11. **Nutrition and Bone Health, Second Edition**, edited by Michael F. Holick and Jeri W. Nieves, 2015

12. **Branched Chain Amino Acids in Clinical Nutrition, Volume 2**, edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
13. **Branched Chain Amino Acids in Clinical Nutrition, Volume 1**, edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
14. **Fructose, High Fructose Corn Syrup, Sucrose and Health**, edited by James M. Rippe, 2014
15. **Handbook of Clinical Nutrition and Aging, Third Edition**, edited by Connie Watkins Bales, Julie L. Locher and Edward Saltzman, 2014
16. **Nutrition and Pediatric Pulmonary Disease**, edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
17. **Integrative Weight Management** edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin and Dr. Laura E. Matarese, 2014
18. **Nutrition in Kidney Disease, Second Edition** edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes and Dr. Glenn M. Chertow, 2014
19. **Handbook of Food Fortification and Health, volume I** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
20. **Handbook of Food Fortification and Health, volume II** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
21. **Diet Quality: An Evidence-Based Approach**, **volume I** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
22. **Diet Quality: An Evidence-Based Approach**, **volume II** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
23. **The Handbook of Clinical Nutrition and Stroke,** edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, M.D., FACP, FACN, FACG, 2013
24. **Nutrition in Infancy**, **volume I** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013
25. **Nutrition in Infancy**, **volume II** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013
26. **Carotenoids and Human Health**, edited by Dr. Sherry A. Tanumihardjo, 2013
27. **Bioactive Dietary Factors and Plant Extracts in Dermatology**, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
28. **Omega 6/3 Fatty Acids**, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
29. **Nutrition in Pediatric Pulmonary Disease**, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
30. **Nutrition and Diet in Menopause**, edited by Dr. Caroline J. Hollins Martin, Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2013.
31. **Magnesium and Health**, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
32. **Alcohol, Nutrition and Health Consequences**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
33. **Nutritional Health, Strategies for Disease Prevention, Third Edition**, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
34. **Chocolate in Health and Nutrition**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
35. **Iron Physiology and Pathophysiology in Humans**, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included **Vitamin D, Second Edition** edited by Dr. Michael Holick; "**Dietary Components and Immune Function**" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi and Dr. Victor R. Preedy; "**Bioactive Compounds and Cancer**" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "**Modern Dietary Fat Intakes in Disease Promotion**" edited by

Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "**Iron Deficiency and Overload**" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "**Nutrition Guide for Physician**s" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple and Dr. Mary Struble; "**Nutrition and Metabolism**" edited by Dr. Christos Mantzoros and "**Fluid and Electrolytes in Pediatrics**" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: "**Handbook of Drug-Nutrient Interactions**" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "**Probiotics in Pediatric Medicine**" edited by Dr. Sonia Michail and Dr. Philip Sherman; "**Handbook of Nutrition and Pregnancy**" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch and Dr. Elliot Philipson; "**Nutrition and Rheumatic Disease**" edited by Dr. Laura Coleman; "**Nutrition and Kidney Disease**" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes and Dr. Glenn Chertow; "**Nutrition and Health in Developing Countries**" edited by Dr. Richard Semba and Dr. Martin Bloem; "**Calcium in Human Health**" edited by Dr. Robert Heaney and Dr. Connie Weaver and "**Nutrition and Bone Health**" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC, and is the editor of ten books including "**Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition**" co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the Journal of Nutrition in Gerontology and Geriatrics, and Antioxidants, and has served as Associate Editor for "Nutrition" the International Journal; served on the Editorial Board of the Journal of Women's Health and Gender-based Medicine, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has co-authored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

Connie W. Bales, Ph.D., R.D., is Professor of Medicine in the Division of Geriatrics, Department of Medicine, at the Duke School of Medicine and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University Medical Center. She is also Associate Director for Education/Evaluation of the Geriatrics Research, Education, and Clinical Center at the Durham VA Medical Center. Dr. Bales is a well-recognized expert in the field of nutrition, chronic disease, function, and aging. Over the past two decades her laboratory at Duke has explored many different aspects of diet and activity as determinants of health during the latter half of the adult life course. Her current research focuses primarily on the impact of protein-enhanced

meals on muscle quality, function, and other health indicators during obesity reduction in older adults with functional limitations. Dr. Bales has served on NIH and USDA grant review panels and is a member of the American Society for Nutrition's Medical Nutrition Council. Dr. Bales has edited three editions of the *Handbook of Clinical Nutrition in Aging* and is Editor-in-Chief of the *Journal of Nutrition in Gerontology and Geriatrics*.

About the Editors

Dr. Rajkumar Rajendram AKC B.Sc. (Hons) MBBS (Dist) MRCP (UK) FRCA EDIC FFICM
Consultant in Internal Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Visiting Lecturer, Division of Diabetes and Nutritional Sciences, King's College London.

Dr. Rajkumar Rajendram is a clinician scientist whose focus is on peri-operative medicine, anaesthesia, intensive care. One of the many aspects of his role is the management of maternal diabetes and nutrition. Dr. Rajendram graduated in 2001 with a distinction from Guy's, King's and St. Thomas Medical School, in London. As an undergraduate he was awarded several prizes, merits and distinctions in pre-clinical and clinical subjects.

Dr. Rajendram began his postgraduate medical training in general medicine and intensive care in Oxford. He attained membership of the Royal College of Physicians (MRCP) in 2004 and completed specialist training in acute and general medicine in Oxford in 2010. Dr. Rajendram also trained in anaesthesia and intensive care in London and became a fellow of the Royal College of Anaesthetists (FRCA) in 2009. He has completed advanced training in regional anaesthesia and intensive care. He became a fellow of the Faculty of Intensive Care Medicine (FFICM) in 2013 and obtained the European diploma of intensive care medicine (EDIC) in 2014.

Dr. Rajendram returned to Oxford as a Consultant in General Medicine at the John Radcliffe Hospital, Oxford before moving to the Royal Free London Hospitals as a Consultant in Intensive Care, Anaesthesia and Peri-operative Medicine. He is currently a Consultant in Internal and Perioperative Medicine at King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Dr. Rajendram recognizes that nutritional support is a fundamental aspect of peri-operative medicine. As a clinician scientist he has therefore devoted significant time and effort into nutritional science research. As a visiting lecturer in the Division of Diabetes and Nutritional Sciences, King's College London he has published over 100 textbook chapters, review articles, peer-reviewed papers and abstracts.

Victor R. Preedy B.Sc., Ph.D., D.Sc., FRSB, FRSPH, FRCPath, FRSC is a staff member of the Faculty of Life Sciences and Medicine within King's College London. He is also a member of the Division of Diabetes and Nutritional Sciences (research) and the Department of Nutrition and Dietetics (teaching). He is also Director of the Genomics Centre of King's College London.

Professor Preedy graduated in 1974 with an Honours Degree in Biology and Physiology with Pharmacology. He gained his University of London Ph.D. in 1981. In 1992, he received his Membership of the Royal College of Pathologists and in 1993 he gained his second doctorate (D.Sc.), for his outstanding contribution to protein metabolism in health and disease. Professor Preedy was elected as a Fellow to the Institute of Biology in 1995 and to the Royal College of Pathologists in 2000. Since then he has been elected as a Fellow to the Royal Society for the Promotion of Health (2004) and The Royal Institute of Public Health (2004). In 2009, Prof. Preedy became a Fellow of the

Royal Society for Public Health and in 2012 a Fellow of the Royal Society of Chemistry. Professor Preedy has carried out research at the National Heart Hospital (part of Imperial College London), The School of Pharmacy (now part of University College London) and the MRC Centre at Northwick Park Hospital. He has collaborated with research groups in Finland, Japan, Australia, USA and Germany. Professor Preedy is a leading expert on the science of health and has a long-standing interest in nutrition and metabolic diseases including diabetes. He has lectured nationally and internationally. To his credit, Prof. Preedy has published over 600 articles, which includes peer-reviewed manuscripts based on original research, abstracts and symposium presentations, reviews and numerous books and volumes.

Dr. Vinood B. Patel, B.Sc., Ph.D., FRSC is a Reader in Clinical Biochemistry at the University of Westminster and honorary fellow at King's College London. Dr. Patel graduated from the University of Portsmouth with a degree in Pharmacology and completed his Ph.D. in protein metabolism from King's College London in 1997. His postdoctoral work was carried out at Wake Forest University Baptist Medical School studying structural-functional alterations to mitochondrial ribosomes, where he developed novel techniques to characterize their biophysical properties. Dr. Patel is a nationally and internationally recognized scientist and in 2014 he was elected as a Fellow to The Royal Society of Chemistry. He presently directs studies on metabolic pathways involved in tissue pathology particularly related to mitochondrial energy regulation and cell death. His research is on studying the role of nutrients, antioxidants, phytochemicals, iron, alcohol and fatty acids in tissue pathology. His other areas of interest include identifying new biomarkers that can be used for diagnosis and prognosis of liver disease, understanding mitochondrial oxidative stress in Alzheimer's disease and gastrointestinal dysfunction in autism. Dr. Patel has edited biomedical books in the area of nutrition and health prevention, autism, biomarkers and has published over 150 articles.

Contact Details: Dr. Vinood Patel, Reader in Clinical Biochemistry, Course Leader for MSc Clinical Biochemistry, Department of Biomedical Science, Faculty of Science & Technology, University of Westminster, 115 New Cavendish Street, London, W1W 6UW, UK. Tel: (+44) (0) 20 35064138, Fax: (+44) (0) 207 911 5087, Email: v.b.patel@westminster.ac.uk

Acknowledgements

The development of this book is built upon the foundation of the excellent work provided by the staff of Humana and Springer-Nature. In particular we wish to acknowledge the outstanding support, advice and great patience of the Series Editor, Dr. Adrianne Bendich, The Developmental Editor, Michael Griffin and Assistant Editor, Samantha Lonuzzi.

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel

Contents

List of Contributors

M. Aguilar-Diosdado, MD, PhD Department of Endocrinology and Nutrition, Puerta del Mar University Hospital, Cadiz, Spain

Charlotte Alexander, BA, MS Department of Obstetrics and Gynecology, "Soroka" University Medical Center, Ben-Gurion University of the Negev, Be'er Sheva, Israel

Habiba I. Ali, PhD, RD, CDE Nutrition and Health Department, College of Food and Agriculture, United Arab Emirates University, Al Ain, United Arab Emirates

Henrik Ullits Andersen, MD, DMSc Steno Diabetes Center Copenhagen, Gentofte, Denmark

João R. Araújo, PhD INSERM U1202, Unité de Pathogénie Microbienne Moléculaire, Institut Pasteur, Paris, France

Björg Ásbjörnsdóttir, MD, DMSc Department of Endocrinology PE7831, Center for Pregnant Women with Diabetes, Faculty of Health and Medical Sciences, Rigshospitalet University Hospital of Copenhagen, University of Copenhagen, Copenhagen, Denmark

Suleyman Aydin, PhD Department of Medical Biochemistry and Clinical Biochemistry (Firat Hormones Research Group), Firat University School of Medicine, Elazig, Turkey

Jean-Marc Ayoubi, MD, PhD Department of Gynecology and Obstetrics, Hôpital Foch, Suresnes, France

Philip Baker, BMedSci, BM, BS, DM, FRCOG, FRCSC, FRANZCOG, FMedSci College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester, UK

Coral Barbas, PhD Facultad de Farmacia, CEMBIO (Center for Metabolomics and Bioanalysis), Universidad CEU San Pablo, Madrid, Spain

Beatriz Barquiel, MD, PhD Diabetes Unit and Endocrinology Department, La Paz University Hospital, Madrid, Spain

Helen L. Barrett, BSc (Hon), MBBS (Hon), PhD School of Medicine, The UQ Centre for Clinical Research, The University of Queensland, Herston, QLD, Australia

Lourdes Basurto, PhD Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Mexico City, Mexico

Malcolm Battin, MB, ChB, MD, FRACP, MRCP(UK), FRCPCH, MPH(Hons) Newborn Services, Auckland City Hospital & Department of Paediatrics, University of Auckland, Auckland, New Zealand

Olga Beltcheva, PhD Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria

Maria Boyadzhieva, MD, PhD Clinical Center of Endocrinology, USBALE "Acad. Iv. Pentchev", Medical University of Sofia, Sofia, Bulgaria

Antonio Brunetti, MD, PhD Department of Health Sciences, University "Magna Græcia" of Catanzaro, Catanzaro, Italy

Leonie K. Callaway, MBBS, PhD, Grad Cert (Leadership) Faculty of Medicine, School of Medicine, RBWH Clinical School, The UQ Centre for Clinical Research, The University of Queensland, Herston, QLD, Australia

Xiaopei Cao, MD, PhD Department of Endocrinology, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Eusebio Chiefari, MD, PhD Department of Health Sciences, University "Magna Græcia" of Catanzaro, Catanzaro, Italy

Stephen Colagiuri, MD The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, The University of Sydney, Sydney, Camperdown, NSW, Australia

Clare E. Collins, PhD, Dip ClinEpi, BSc, Dip N&D Priority Research Centre in Physical Activity and Nutrition, School of Health Sciences, University of Newcastle, Callaghan, NSW, Australia; Nutrition and Dietetics, School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia

Francesco Corrado, MD Department of Obstetrics and Gynecology, A.O.U. Policlinico "G. Martino", Policlinico Universitario, University of Messina, Messina, Italy

Donald R. Coustan, MD Warren Alpert Medical School of Brown University, Providence, USA; Attending Maternal-Fetal Medicine Specialist, Women & Infants Hospital of Rhode Island, Providence, RI, USA

Rosario D'Anna, MD Department of Human Pathology and Development, "Gaetano Martino" University Hospital, University of Messina, Messina, Italy

Hannah Grace Dahlen RN, RM, BN (Hons), Grad Cert Mid (Pharm) MCommN, PhD, FACM School of Nursing and Midwifery, Western Sydney University, Penrith, NSW, Australia; Ingham Institute, Liverpool, NSW, Australia

Peter Damm, MD, DMSc Department of Obstetrics, Center for Pregnant Women with Diabetes, Copenhagen, Denmark; Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

H. David McIntyre, MBBS, MD Faculty of Medicine, Mater Clinical School, The University of Queensland, South Brisbane, QLD, Australia

Jamie V. de Seymour, BSc, PhD candidate in biomedical sciences Liggins Institute, The University of Auckland, Grafton, Auckland, New Zealand

Evanthia Diamanti Kandarakis, MD, PhD Department of Endocrinology and Center of Excellence in Diabetes and Metabolic Diseases, Athens Euroclinic, University of Athens Medical School, Athens, Greece; Department of Endocrinology and Diabetes Center of Excellence, EUROCLINIC, Athens, Greece

Danuta Dudzik, PhD Facultad de Farmacia, CEMBIO (Center for Metabolomics and Bioanalysis), Universidad CEU San Pablo, Madrid, Spain

Fidelma P. Dunne, MB BCh BAO, MD, PhD Department of Medicine, National University of Ireland Galway, Galway, Ireland

Aoife M. Egan, MB BCh BAO Department of Medicine, National University of Ireland Galway, Galway, Ireland

Luisa F. Gomez Arango, MSc School of Medicine, The UQ Centre for Clinical Research, The University of Queensland, Herston, QLD, Australia

Leonor Guariguata, BA, MPH Brussels, Belgium

Kym J. Guelfi, BSc(Hons) PhD School of Sport Science, Exercise and Health, The University of Western Australia, Perth, WA, Australia

Gil Gutvirtz, MD Department of Obstetrics and Gynecology, "Soroka" University Medical Center, Ben-Gurion University of the Negev, Be'er Sheva, Israel

Rhiannon E. Halse, BSc(Hons), PhD School of Nutrition, Dietetics and Food Technology, Curtin University, Perth, WA, Australia

Marcelino Hernandez, PhD Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Mexico City, Mexico

Marta Hernandez, MD Department of Endocrinology and Nutrition, Institut de Recerca Biomèdica de Lleida (IRBLleida), Hospital Universitari Arnau de Vilanova, Lleida, Spain

Teri L. Hernandez, PhD, RN Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, University of Colorado, Aurora, CO, USA

Isabelle Hininger-Favier, PhD Department of Biology and Nutrition, Faculty of Pharmacy, INSERM U1055, Laboratory of Fundamental and Applied Bioenergetics (LBFA), Université Grenoble Alpes, Grenoble, France

Ioannis Ilias, MD, PhD Endocrine Unit, Elena Venizelou Hospital, Athens, GR, Greece

Radka Kaneva, PhD Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria

Ritsuko Kawaharada, PhD Department of Nutrition, Faculty of Health and Welfare, Takasaki University of Health and Welfare, Takasaki, Gunma, Japan

Elisa Keating, PhD Department of Biochemistry, Faculty of Medicine, CINTESIS, Center for Research in Health Technologies and Information Systems, University of Porto, Porto, Portugal

Eftychia Koukkou, MD, PhD Endocrine Unit, Elena Venizelou Hospital, Athens, GR, Greece

Rossella Liguori, MD Department of Health Sciences, University "Magna Græcia" of Catanzaro, Catanzaro, Italy

Ute Linnenkamp, MPH International Diabetes Federation, Deutsches Diabetes-Zentrum (DDZ), Paul-Langerhans-Gruppe, für Versorgungsforschung und Gesundheitsökonomie, Düsseldorf, Germany; International Diabetes Federation, Brussels, Belgium

C. López-Tinoco, MD, PhD Department of Endocrinology and Nutrition, Puerta del Mar University Hospital, Cadiz, Spain

Lesley MacDonald-Wicks, PhD, BHSc, GCTT Nutrition and Dietetics, School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia

Lydia Elizabeth Makaroff, MPH, PhD International Diabetes Federation, Brussels, Belgium

Fátima Martel, PhD Department of Biochemistry, Faculty of Medicine, Institute for Research and Innovation in Health Sciences, University of Porto, Porto, Portugal

Elisabeth R. Mathiesen, MD, DMSc Department of Endocrinology PE7831, Faculty of Health and Medical Sciences, Center for Pregnant Women with Diabetes, Rigshospitalet University Hospital of Copenhagen, University of Copenhagen, Copenhagen, Denmark

Dídac Mauricio, MD, PhD Department of Endocrinology and Nutrition, CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Hospital Universitari Germans Trias I Pujol, Badalona, Spain

Elizabeth McKenzie, PhD (Forensic Science) Liggins Institute, The University of Auckland, Grafton, Auckland, New Zealand

Patricia Mendoza, PhD Laboratory of Molecular Biology and Pharmacogenomics, Juarez Autonomous University of Tabasco, Cunduacan, Tabasco, Mexico

Najoua El Mesmoudi, MSc Nutrition and Health Department, College of Food and Agriculture, United Arab Emirates University, Al Ain, United Arab Emirates

Vanio Mitev, MD, PhD, DSs Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria

Lida Moghaddam-Banaem, MD, PhD Department of Midwifery and Reproductive Health, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

Cristina Moreno-Castilla, MSc, RD Department of Endocrinology and Nutrition, Hospital Universitari Arnau de Vilanova, Lleida, Spain

Jean-Marc Moulis, PhD Department of Biology and Nutrition, Faculty of Pharmacy , INSERM U1055, Laboratory of Fundamental and Applied Bioenergetics (LBFA), Université Grenoble Alpes, Grenoble, France; Bioscience and Biotechnology Institute (BIG), CEA, Grenoble, France

Akio Nakamura, PhD Department of Molecular Pharmacology and Oncology, School of Medicine, Gunma University, Maebashi, Gunma, Japan

John P. Newnham, MBBS, MD, W.Aust., FRCOG, FRANZCOG, DDU, CMFM School of Women's and Infants' Health, The University of Western Australia, Perth, WA, Australia

Marloes Dekker Nitert, MSc, Med. Lic, PhD, Grad Cert (Clinical Trials) School of Medicine, The UQ Centre for Clinical Research, The University of Queensland, Herston, QLD, Australia

Katherine Ogurtsova, PhD International Diabetes Federation, Brussels, Belgium; Deutsches Diabetes-Zentrum (DDZ), Paul-Langerhans-Gruppe für Versorgungsforschung und Gesundheitsökonomie, Düsseldorf, Germany

Patricia Ostrosky, PhD Department of Genomic Medicine and Environmental Toxicology, Instituto de Investigaciones Biomedicas, Autonomous National University of Mexico, Mexico City, Mexico

Emilia Papakonstantinou, PhD, RD Department of Food Science and Human Nutrition, Agricultural University of Athens, Athens, Greece

Paola Parra, MD Diabetes Unit and Endocrinology Department, La Paz University Hospital, Madrid, Spain

Ida Pastore, MD Department of Health Sciences, University "Magna Græcia" of Catanzaro, Catanzaro, Italy

Vinood B. Patel, BSc, PhD Department of Biomedical Sciences, Faculty of Science and Technology, University of Westminster, London, UK

Bengt Persson, MD, PhD Karolinska Institutet, Stockholm, Sweden

Martina Persson, MD, PhD Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; Diabetes and Endocrinology, Sachsska Children's Hospital, Stockholm, Sweden

Basilio Pintaudi, MD Diabetic Unit, Niguarda Cà Granda, A.O. Ca' Granda Niguarda, Milano, Italy

Victor R. Preedy, BSc, PhD, DSc Department of Nutrition and Dietetics, Nutritional Sciences Division, School of Biomedical and Health Sciences, King's College London, London, UK

Edgardo Puello, MD Hospital of Gynecology and Obstetrics, Medical Center La Raza, Mexican Social Security Institute, Mexico City, Mexico

Rajkumar Rajendram, AKC, BSc (Hons), MBBS (Dist), MRCP (UK), FRCA, EDIC, FFICM Department of Nutrition and Dietetics, Nutritional Sciences Division, School of Biomedical and Health Sciences, King's College London, London, UK

Amutha Ramadas, PhD (Public Health); MSc (Clinical Nutrition); BSc (Nutrition & Community Health) Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

M. Pilar Ramos, PhD Biochemistry and Molecular Biology, Facultad de Farmacia, Universidad CEU San Pablo, Madrid, Spain

Lene Ringholm, MD, PhD Steno Diabetes Center Copenhagen, Gentofte, Denmark

M.M. Roca-Rodríguez, MD, PhD Department of Endocrinology and Nutrition, Puerta del Mar University Hospital, Cadiz, Spain

Janet Rowan, MBChB, FRACP National Women's Health, Auckland City Hospital, Auckland, New Zealand

Angelo Santamaria, MD Department of Human Pathology and Development, "Gaetano Martino" University Hospital, University of Messina, Messina, Italy

Renata Saucedo, PhD Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Mexico City, Mexico

Eyal Sheiner, MD, PhD Department of Obstetrics and Gynecology, "Soroka" University Medical Center, Ben-Gurion University of the Negev, Be'er Sheva, Israel

Sangeetha Shyam, PhD (Medical and Health Sciences), MSc (Foods and Nutrition), BSc (Nutrition and Dietetics) Division of Nutrition and Dietetics, School of Health Sciences, International Medical University, Bukit Jalil, Kuala Lumpur, Malaysia

Helen M. Taylor, GC DiabEd&MGMT, MPH, BSc, PhD Candidate Priority Research Centre in Physical Activity and Nutrition, School of Health Sciences, University of Newcastle, Callaghan, NSW, Australia

Charlene Thornton, BN, Grad.Dip.Mid, MSc Med (Research), MSc Med (Clin Epi), PhD School of Nursing and Midwifery, Western Sydney University, Penrith, NSW, Australia

Anastasia Trouva, MD, PhD-student Department of Molecular Medicine and Surgery, Karolinska Institutet, Solna, Sweden; Center for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden

Jorge Valencia, PhD Candidate Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Mexico City, Mexico

Trecia A. Wouldes, BA, MA, PhD Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Haipeng Xiao, MD, PhD Department of Endocrinology, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Sununta Youngwanichsetha, PhD Department of Obstetric-Gynecologic Nursing and Midwifery, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Arturo Zarate, PhD Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Mexico City, Mexico

Jing Zhou, MD Department of Endocrinology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Part I
Definitions, Characterization and Diagnosis

Chapter 1
Global Estimates of Hyperglycaemia in Pregnancy: Determinants and Trends

Leonor Guariguata, Ute Linnenkamp, Lydia Elizabeth Makaroff, Katherine Ogurtsova and Stephen Colagiuri

Key Points

- Hyperglycaemia in pregnancy is a large and growing burden in global health.
- Changes in the definition of hyperglycaemia in pregnancy affect the way the burden is quantified.
- Shifting demographics towards lower fertility and longer survival will put more women at risk of hyperglycaemia in pregnancy, especially in developing countries.
- Shifting patterns in disease from infectious to non-communicable disease will increase the risk of developing hyperglycaemia in pregnancy for women.
- There are regional variations in the burden of hyperglycaemia in pregnancy but the burden is high all over the world.
- A comprehensive public health response is required to reduce the consequences and prevent new cases of hyperglycaemia in pregnancy.

Keywords Epidemiology · Hyperglycaemia in pregnancy · Developing countries · Pregnancy and diabetes · Global estimates

L. Guariguata (✉)
Rue Sainte Gertrude 3, Chausée de la Hulpe 166, Brussels, Belgium
e-mail: leonor.guariguata@gmail.com

U. Linnenkamp
International Diabetes Federation, Deutsches Diabetes-Zentrum (DDZ), Paul-Langerhans-Gruppe, für Versorgungsforschung und Gesundheitsökonomie, Auf´m Hennekamp 65, Düsseldorf, Germany
e-mail: ute_linnenkamp@gmx.de

U. Linnenkamp · L.E. Makaroff · K. Ogurtsova
International Diabetes Federation, Chaussée de la Hulpe 166, Brussels, Belgium
e-mail: lydia.makaroff@gmail.com

K. Ogurtsova
e-mail: kogurtsova@gmail.com

K. Ogurtsova
Deutsches Diabetes-Zentrum (DDZ), Paul-Langerhans-Gruppe für Versorgungsforschung und Gesundheitsökonomie, Auf´m Hennekamp 65, Düsseldorf, Germany

S. Colagiuri
The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, The University of Sydney, Level 2 Charles Perkins Centre D17, Johns Hopkins Drive (off Missenden Road), Sydney, Camperdown, NSW, Australia
e-mail: stephen.colagiuri@sydney.edu.au

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_1

Abbreviations

DIP	Diabetes in pregnancy
GDM	Gestational diabetes
HFDP	Hyperglycaemia first detected during pregnancy
HIP	Hyperglycaemia in pregnancy
IDF	International Diabetes Federation
NCD	Non-communicable disease
NDDG	National Diabetes Data Group
OGTT	Oral glucose tolerance test
TDP	Total diabetes in pregnancy
WHO	World Health Organization

Introduction

Diabetes is a serious and growing disease with implications for health and development. More than 400 million people have diabetes [1, 2]. While the majority of cases consist of type 2 diabetes, hyperglycaemia and diabetes in pregnancy and their outcomes present a serious and increasing global challenge [3]. Babies born to women with elevated blood glucose levels are at greater risk of adverse pregnancy outcomes including foetal abnormalities, macrosomia, obstructed labour, and hyperinsulinemia and hypoglycaemia at birth [4]. Even with the mildest forms of hyperglycaemia in pregnancy (HIP), both mother and child are at increased risk of later development of type 2 diabetes, carrying on the diabetes epidemic through future generations [5].

Estimating the global burden of HIP is a challenge because of the variety of methods and definitions used [6]. However, the public health importance of HIP is high and understanding the direction of the epidemic and those most vulnerable is essential to beginning the important work of turning the tide on diabetes.

Defining Hyperglycaemia in Pregnancy, Risk Factors and Outcomes

Various national and international bodies have published a range of guidelines and recommendations on screening methods and diagnostic criteria for the screening and diagnosis of HIP. The condition was first known only as gestational diabetes mellitus (GDM) and was described for mothers developing hyperglycaemia during their pregnancies. The first diagnostic criterion was provided by O'Sullivan et al. in 1964 and was based on 3-h 100 g oral glucose tolerance test (OGTT) at 22 weeks gestation [7]. The hyperglycaemia would inevitably resolve post-partum. The criterion was validated against the risk of future development of diabetes for the mothers and gained wide acceptance. At the time, developing type 2 diabetes in women of reproductive age was so rare as to be unconsidered in the development of a definition.

In 1980, the World Health Organization (WHO) made the recommendation to use a 2-h 75 g OGTT for pregnant women to harmonise the diagnostic criteria with that used to diagnose diabetes and impaired glucose tolerance [8]. Since the 2-h 75 g OGTT had been little investigated for use in pregnancy, various associations and national guideline panels stayed with the recommendations of the U.S. National Diabetes Data Group (NDDG) to use the O'Sullivan 3-h test [9]. However, the different associations chose different blood glucose thresholds to detect abnormalities in pregnancy due to

difficulties associated with converting glucose values from O'Sullivan's studies to their equivalents when glucose was analysed using modern methods in plasma. The result for epidemiology was a variety of studies reporting wildly different estimates and confusion for clinicians on how to define the condition.

There is a dose effect on the developing foetus of increases in blood glucose. Relatively mild hyperglycaemia may lead to less serious outcomes such as macrosomia while early exposure to high blood glucose can lead to birth defects and spontaneous abortion [4]. As more and more women of reproductive age started to develop type 2 diabetes, it became important to distinguish between pre-existing but undiagnosed diabetes in pregnancy from the milder form that develops at 22 weeks and resolves post-partum.

Under the first definition of GDM, a number of studies identified potential risk factors as a way of selecting women for screening, particularly in low-resource settings where universal screening is not feasible. The most important risk factors to emerge were obesity, high blood glucose prior to pregnancy, a family history of diabetes, a history of GDM in previous pregnancy, a history of large for gestational age baby in a previous pregnancy, increasing age, excessive weight gain during pregnancy, and a history of stillbirth or congenital abnormality in the infant [10, 11]. There is considerable overlap in these risk factors with those for type 2 diabetes, which may indicate that a substantial proportion of what was categorised as GDM, was in fact pre-existing diabetes. The identification of a risk profile for screening was further complicated by the fact that many women with risk factors for GDM never developed the condition and similarly many with a low-risk profile later presented with GDM [12, 13].

Experts in the field realised that the most effective way of defining GDM and distinguishing it from pre-existing diabetes in pregnancy was to focus on outcomes. In 2008, the Hyperglycaemia and Adverse Pregnancy Outcomes [4] study tested 25,505 pregnant women in an international multi-centre study using a 2-h 75 g OGTT and followed them through pregnancy. The results lead to recommended diagnostic criteria for GDM representing the average glucose values at which the odds for birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percentage body fat >90th percentile reached 1.75 times the odds of these outcomes [14]. The thresholds established by this study were adopted by many guidelines and were also recommended by the American Diabetes Association in its 2011 position statement [15].

Most recently, in 2013 the World Health Organization proposed new criteria for the diagnosis and definition of hyperglycaemia first detected in pregnancy. The definition distinguishes the more serious diabetes in pregnancy (DIP), which is more likely to persist beyond the birth and can cause serious foetal abnormalities early in pregnancy, from the milder gestational diabetes (GDM) [16]. The new definition calls for an understanding of the burden of HIP and its relationship with the growing epidemic of type 2 diabetes and distinguishes DIP from GDM based on the degree of hyperglycaemia; a reflection that the risk of serious complications is much higher in diabetes in pregnancy than in GDM. Where studies previously reported the prevalence of GDM, under the new definition, these figures would also include the more severe hyperglycaemia classified as diabetes in pregnancy under the broad title of hyperglycaemia first detected in pregnancy (HFDP) (Table 1.1). Added to this definition are women with diagnosed diabetes who become pregnant; the term HIP encompasses the burden of any glucose intolerance in pregnancy.

Estimating the Burden of HIP

With a clear definition established and risk factors outlined, tracking the burden of HIP becomes more feasible. Some of the most important contributors to the diabetes epidemic, population ageing and changes towards the so-called 'obesogenic' lifestyle, are also contributing to the growing burden of HIP.

Table 1.1 Terminology defining hyperglycaemia in pregnancy and related conditions

Term	Definition
Hyperglycaemia in pregnancy (HIP)	Includes hyperglycaemia first detected during pregnancy (HFDP), and live births in women with previously diagnosed diabetes
Total diabetes in pregnancy (TDP)	Includes live births in women with previously diagnosed diabetes and in women with diabetes in pregnancy
Hyperglycaemia first detected during pregnancy (HFDP)	Includes diabetes in pregnancy (DIP) and gestational diabetes (GDM) as per the WHO 2013 definition
Diabetes in pregnancy (DIP)	Includes: pregnancy in women with previously undiagnosed diabetes; at anytime during pregnancy a fasting plasma glucose >7.0 mmol/L (126 mg/dL); or 2-h plasma glucose >11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load (OGTT); or random plasma glucose >11.1 mmol/L and diabetes symptoms
Gestational diabetes (GDM)	At anytime during pregnancy a fasting plasma glucose 5.1–6.9 mmol/L (92–125 mg/dL); or 1-h plasma glucose >10.0 mmol/L (180 mg/dL) following a 75 g oral glucose load; or 2-h plasma glucose 8.5–11.0 mmol/L (153–199 mg/dL) following a 75 g oral glucose load (OGTT)

Data source [37]

Each of these contributors is described in turn followed by a discussion of the global and regional prevalence estimates for HIP as well as especially vulnerable populations. Finally, a discussion of future trends and projections for HIP and the public health response concludes the chapter.

The Demographic Transition

In 2012, the United Nations estimated that the global population had reached 7 billion people [17]. Population growth has been on an exponential curve with rapid increases in population and shifts towards an older population average age [18]; in just the last decade, the global population has increased by one billion people [19]. The recent period of very rapid demographic change is a result of a secular process called the demographic transition [20]. This transition follows along the development process that transforms a traditional society into an industrial one. A model of the transition is presented in Fig. 1.1. Populations prior to the transition exist with high death rates due to disease and low life expectancy but also high birth and fertility rates to compensate for low survival. Fertility tends to decline as the survival of children into adulthood increases, as family planning becomes more common, and as other competing factors in lifestyle change priorities for women and families on having children. Meanwhile, mortality decreases and increases in life expectancy come with better provision of health services, declines in infectious disease and accompanying deaths in children and young people.

Once the transition begins, the process can be divided in two distinct phases. In the first phase, death rates decline and the birth or fertility rates remain high, leading to an overall growth in the population. In the second phase, fertility rates decline leading to a stabilising or decline in growth over time. Countries have experienced, or are experiencing the demographic transition at different rates and times. Most high-income, developed countries have a large older population that reflects low fertility and high survival (Fig. 1.1). This compares with developing countries for which the demographic transition is in full force.

The demographic transition in fertility and mortality has led to important changes in the global population's age composition (Fig. 1.2). Globally, the population is shifting towards older age groups. The result is an added pressure on health systems to care for the elderly and for the non-communicable diseases (NCDs) associated with age. This in turn has a flow on effect with NCDs

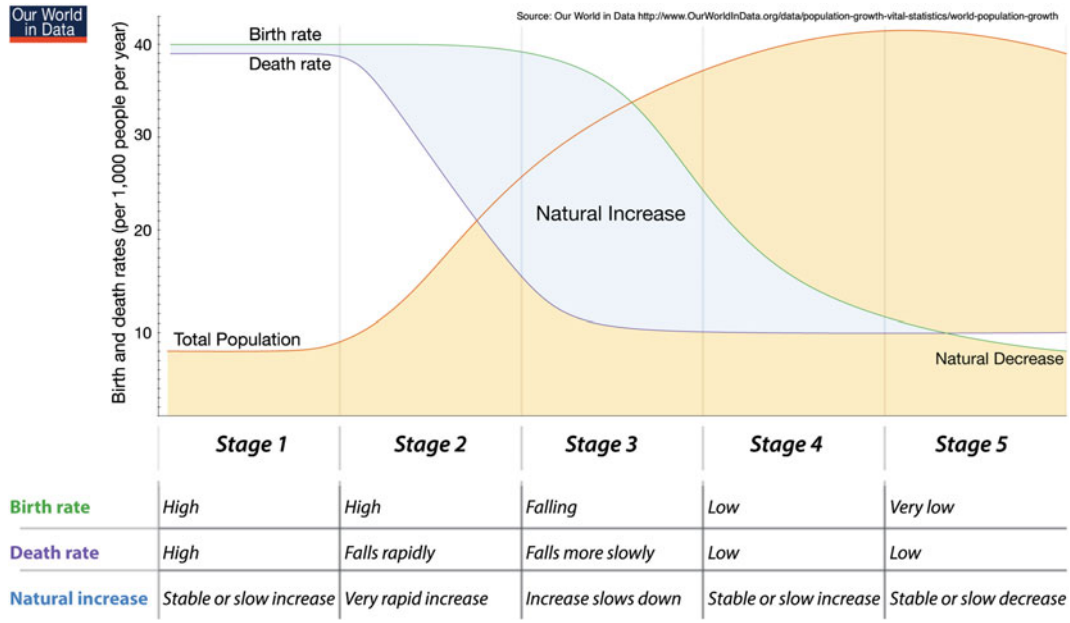


Fig. 1.1 The demographic transition in birth and death rates with effects on the total population. *Source* Our world in data http://www.OurWorldInData.org/data/population-growth-vital-statistics/world-population-growth

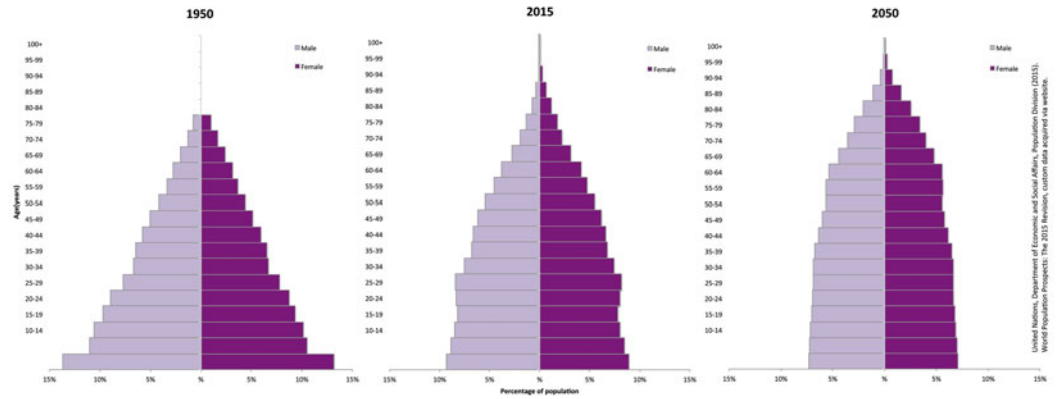


Fig. 1.2 World population distributions by age and sex for 1950, 2015, and 2050. *Data source* United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision, custom data acquired via website

emerging in younger populations and those which increase the risk to future NCDs; among these are gestational diabetes and hyperglycaemia first detected during pregnancy.

High levels of fertility are typically found in countries that also have a high infant mortality and a low use of contraceptives and family planning services [21]. In these societies, families have as many children as they are able to sustain knowing that a number of those children will not reach adulthood. The fertility and mortality rates balance each other in this scenario leading to a relatively stable population.

Further progress in birth control methods and neonatal care, as well as overall development, has shifted fertility downward with the most extreme case of two or even fewer children per woman in Western Europe with few exceptions [22]. This reproductive revolution is mainly due to two factors. First, the desired family size has declined as the cost of having children rose and child survival increased. Second, government intervention played a key role in some parts of the world. In China, for example, this took the form of the one-child policy [23], but many other countries implemented voluntary family planning programmes that provide information and access to contraceptives at subsidised prices [24].

The fertility stage when a woman can get pregnant is narrowing in relation to the total life span. Yet, the pattern of fertility occurring with development is also characterised by shifting of childbirth to older ages in a life course. Women in developed countries are having children later in life, which in turn contributes to a greater proportion of live births after 40 [25]. Changes in fertility may also lead to less children per woman in those countries since less time was left between the birth of the first child and the end of fertility.

The combination of these shifting patterns in demographics and fertility has contributed substantially to increases in HIP. Age is one of the most important risk factors for almost any type of HIP and as women of reproductive age have children at older ages, this will lead to more cases of HIP.

The Epidemiological Transition and the Obesogenic Environment

Trends in health are shifting towards NCDs and away from infectious disease. This phenomenon is known as the 'epidemiological transition' [26]. The transition is characterised by a substantial improvement in child and maternal mortality, a reduction in death and disability from infectious disease, an overall increase in survival and life expectancy, and an increase in NCDs such as cardiovascular disease, diabetes, chronic pulmonary diseases and cancer. Developing countries are experiencing this shift most rapidly and by 2020, NCDs are expected to account for 7 out of 10 deaths in these regions compared with fewer than 5 of 10 deaths today [27]. This shift in the NCD burden, which has important implications for pregnancy, is driven by a shift in the shared core group of risk factors for NCDs: poor diet, low physical activity, tobacco use, and harmful use of alcohol. Most significantly for diabetes and pregnancy, the world population is moving towards a decrease in physical activity and increases in poor diet [28]. The shift contributes to what is known as the 'obesogenic' environment which makes choices for health harder to make and unhealthy behaviours the norm. For developing countries, where the majority of women of reproductive age live, the transition is happening at greater speed [29–31].

The change is driven by a number of factors including changes to the built environment, more people using cars for transportation, and work that requires little physical activity [32]. Where countries are experiencing an epidemiological transition in disease patterns towards NCDs, changes to risk factors like physical activity are also occurring. Sedentary behaviour is considered a risk factor for type 2 diabetes and also for HIP-related conditions like gestational diabetes [33, 34]. It is also a key component of management of women with these conditions. However, it is important to consider that for many women social norms, the environment, or even safety may play a major factor in engaging in physical activity.

One of the major contributors to global increases in high blood glucose, and subsequently HIP, is changes to diet and nutrition. The so-called 'Western diet' is characterised by a high intake of processed foods, sugars, trans fats, and salt. Much of the way in which people eat is shifting away from traditional diets high in fruits and vegetables and towards the Western diet [35]. This has important implications for pregnancy where poor nutrition is a risk factor for the development of high blood glucose. For women who have already developed HIP, a healthy diet and nutrition is an

important part of management of the condition. However, where food availability is skewed towards highly processed, unhealthy food choices changing behaviour at the level of the individual is a significant challenge.

As discussed above, there is significant overlap in the type 2 diabetes epidemic and women developing or being diagnosed with HIP. The drivers of one inevitably drive the other. Where shifts in risk factors for type 2 diabetes and obesity occur and in the absence of prevention, we can expect a concomitant increase in HIP. There is a collision of risk factors as the type 2 diabetes epidemic and its determinants shifts towards younger age groups and fertility rates in women towards older age. The two combined with high birth rates in many developing countries will inevitably mean more women globally faced with high blood glucose during pregnancy.

Estimating HIP

Accurate and comparable estimates of HIP are important not just for monitoring and surveillance, but for public health planning and education of health professionals. The large variation in the definition of HIP and the terminology applied to describe associated conditions has made it difficult to estimate the burden of HIP [6]. Even with a newly adopted WHO definition of HIP [16] that marks clear boundaries in severity for gestational diabetes and hyperglycaemia first detected during pregnancy, it will take years before a unified definition is applied clinically or in epidemiological studies. Part of this may have to do with resources, but also with national standards and even the interests of the investigators.

Nonetheless, the gold standard for building an estimate of disease prevalence is the population-based study. In this study design, the researcher takes a sample of the population that is deemed to be representative of the whole and systematically tests each person within that sample for a given disease or condition. In the case of estimating type 2 diabetes, for example, such population-based studies involve investigators going door to door in the selected sampling area and testing subjects who agree to be included using a blood sample and applying the same procedure to each subject. This allows the investigators to build an estimate of the prevalence for diabetes for that sample and infer what that prevalence may be for the population within certain boundaries or confidence intervals.

Type 2 diabetes is a relatively stable disease in that once a person has developed the condition they will not spontaneously recover or go into remission without treatment. This makes it relatively straightforward to study because the timeframe used to collect data may be quite long. In the case of conditions of pregnancy, such as HIP, timing presents an added challenge. A woman is only pregnant for some months in a year. In addition, some conditions of HIP, such as gestational diabetes, will only develop after a certain point in the pregnancy so that testing is limited to an even shorter timeframe. Ideally, all pregnant women would be followed throughout their pregnancies and screened multiple times, as proscribed by the WHO recommendations: once to rule out previously undiagnosed existing type 2 diabetes early in pregnancy and thus prevent the most serious risks to the developing foetus by early treatment; and, for those who show no hyperglycaemia early in the pregnancy, an additional screening at 24–28 weeks for gestational diabetes. If this approach were universally applied, epidemiologists could simply access results from the health records of screened women to make an estimate of HIP-affected pregnancies in a year. However, universal antenatal care is far from a reality, especially in developing countries [36].

Indeed, very few population-based studies exist [6]. Most studies draw from samples in a group of hospitals or even a single hospital. These studies can hardly be considered representative for an entire country, except where near-universal antenatal care exists. A few countries have come close (e.g. Denmark, Sweden, the Netherlands and others), but for many countries, hospital data are not a

reliable source. The result is that for many parts of the world, there is simply not enough data to make a representative guess of the burden of HIP.

The estimates presented here are a combination of studies selected to be the best or most reliable and then adjusted for differences in definitions, age, and fertility patterns. These were then applied to population estimates to arrive at regional and global estimates of prevalence [3]. Where country estimates exist, studies conducted in those countries were reliable enough to be used.

Global and Regional Estimates, and Vulnerable Populations

The International Diabetes Federation (IDF) estimates that in 2015, 16.2% of live births to women between the ages of 20 and 49 years had some form of HIP (Table 1.1) [37]. The vast majority of those cases are due to the milder form gestational diabetes (85.1%), while the rest represent pre-existing diabetes only about half of which was diagnosed prior to pregnancy. This figure translates to at least 20.9 million live births affected by some form of HIP.

One of the most important risk factors for the development of HIP and especially gestational diabetes is increasing age. As seen in Fig. 1.3, the prevalence of HIP starts at around 10% for women 20–24 years old and increases rapidly to almost half of live births in women over the age of 45 (45.9%). However, as described above, fertility rates move in the opposite direction with many more total live births in younger women and fewer in the older age groups. As a result, the majority of live births affected by HIP occurred in women under the age of 30 (10.4 million). If the estimates included women and girls 15 years and older, the numbers would inevitably be higher. However, reliable data on diabetes prevalence and fertility are not available for many countries for younger age groups. (Table 1.2).

Regional Variation

There are some regional differences in the prevalence of HIP (Table 1.3, Fig. 1.4). In terms of percentage of live births affected, the South-east Asia Region that includes India and Pakistan, had the highest prevalence at 24.2% compared to 10.5% in sub-Saharan Africa (Table 1.3). When factoring in fertility rates for different regions, the numbers of live births show a similar pattern. South-east Asia also had the highest number of live births affected by HIP (6.7 million), followed by the Middle East and North Africa region (3.7 million), and the Western Pacific (3.7 million) including China, Australia and Indonesia. The Americas had the lowest numbers of live births estimated affected by HIP at just under 2 million although still close to 12% of births are affected by HIP.

HIP and Development

The vast majority (87.6%) of cases of HIP were in low- and middle-income countries (Fig. 1.5), where access to antenatal and maternal care is often limited or non-existent. Not coincidentally, middle-income countries also have the highest burden of diabetes in the world [37]. These are areas where demographic, social and epidemiological transitions are rapidly changing lifestyle patterns and fertility. The combination is an increase in life expectancy, but maintaining a high fertility rate coupled with changes in health behaviours including diet and physical activity. The result is an environment highly conducive to the development of HIP, but with a health system that is unlikely to

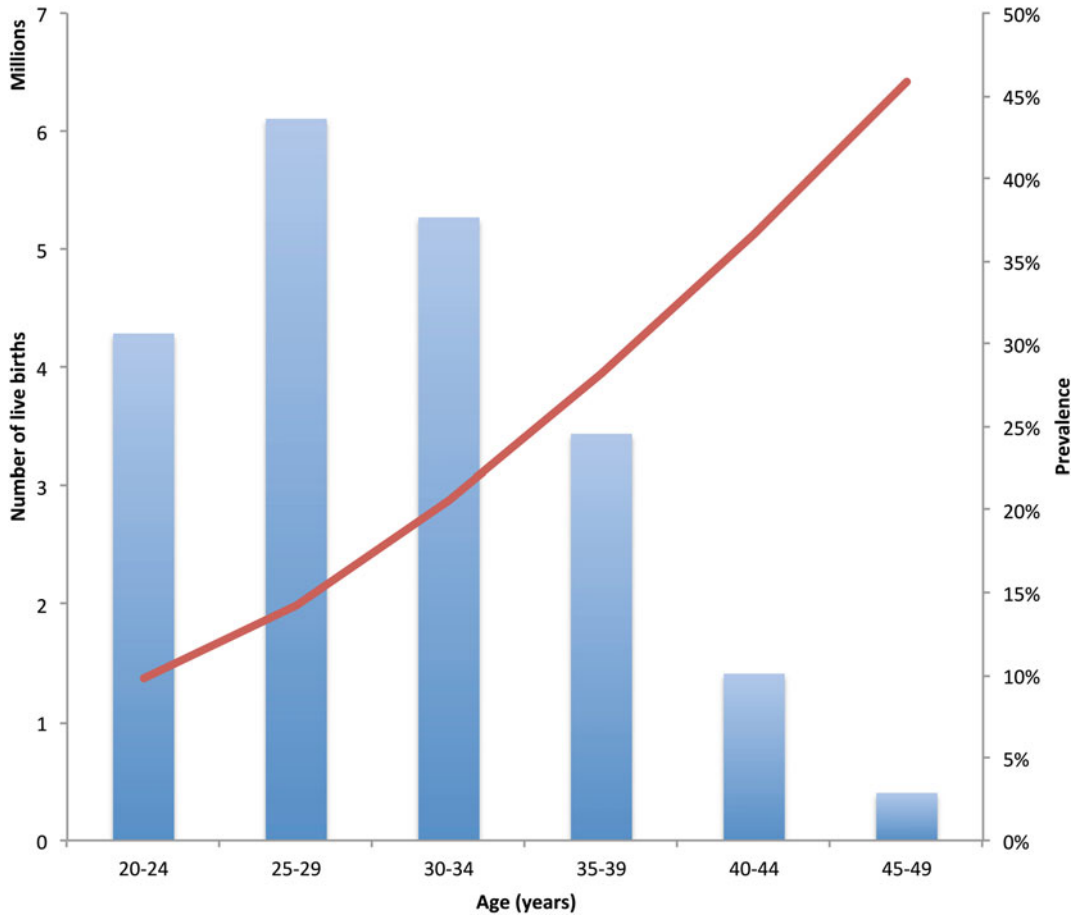


Fig. 1.3 Number of live births affected and prevalence (%) of HIP by age (years) in 2015. *Data source* [37]

Table 1.2 Global estimates of hyperglycaemia in pregnancy, 2015

Total live births to women aged 20–49 years (millions)	129.4
Hyperglycaemia in pregnancy	
Global prevalence (%) of live births	16.2
Number of live births affected (millions)	20.9
Percentage due to gestational diabetes (%)	85.1
Percentage due to diabetes first detected in pregnancy	7.4
Percentage due to previously diagnosed diabetes	7.5

Data source [37]

be able to meet this high burden. Indeed, rapid development in many parts of the world mean that population patterns and disease are shifting more rapidly than the development of health systems or prevention. The most likely scenario is that low-income countries will also follow this pattern, but that it will be many generations before the health systems of these developing countries reach a point where primary and antenatal care are sufficient to stem the burden of HIP and its outcomes.

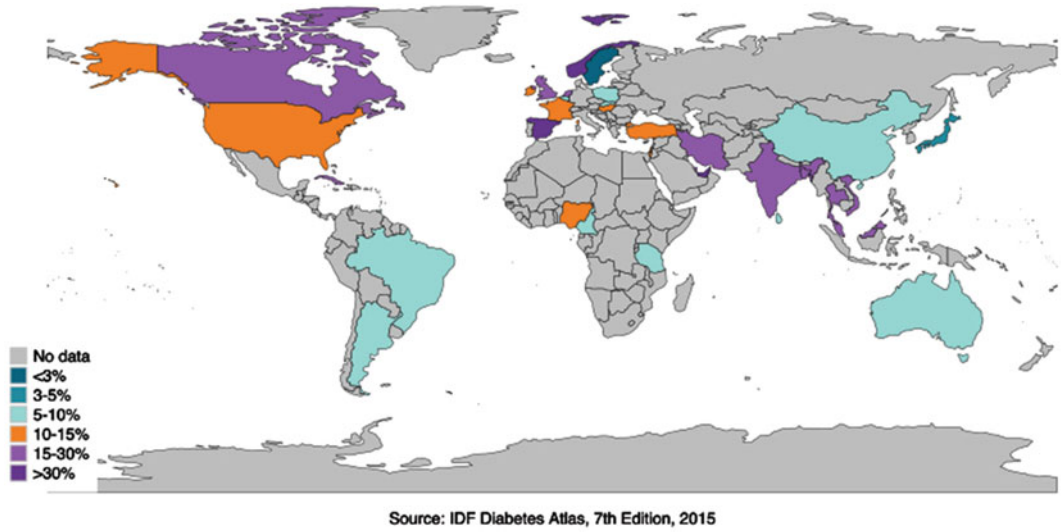


Fig. 1.4 Estimates of prevalence (%) of HIP in the world, 2015

Table 1.3 Hyperglycaemia in pregnancy in women aged 20–49 years by region, 2015

Region	Unadjusted prevalence (%)	Age-adjusted prevalence (%)	Number of live births affected (millions)
Sub-saharan Africa	10.5	9.5	3.3
Europe	15.8	13.7	1.7
Middle East and North Africa	21.8	17.7	3.7
North America and Caribbean	14.9	11.9	1.0
South and Central America	13.2	11.5	0.9
South-east Asia	24.2	26.3	6.7
Western Pacific	12.4	12.1	3.7

Data source [37]

At-Risk Populations and Indigenous Peoples

Variations in the burden of HIP also exist within country borders. Some populations and ethnic groups are developing HIP and gestational diabetes at higher rates [38, 39]. This may be due to genetic predispositions, but also to changes in lifestyle. Indigenous peoples have shown higher prevalence rates of gestational diabetes and also type 2 diabetes when compared to non-indigenous populations in the same country [40].

Many of these populations are at social disadvantage through a lack of economic and social support, education, employment, health and security. As a result, they are not only faced with higher rates of HIP but poorer outcomes associated with a lack of adequate management. Indigenous peoples shoulder a disproportionate burden of diabetes in many parts of the world and this is reflected in the burden of HIP as well.

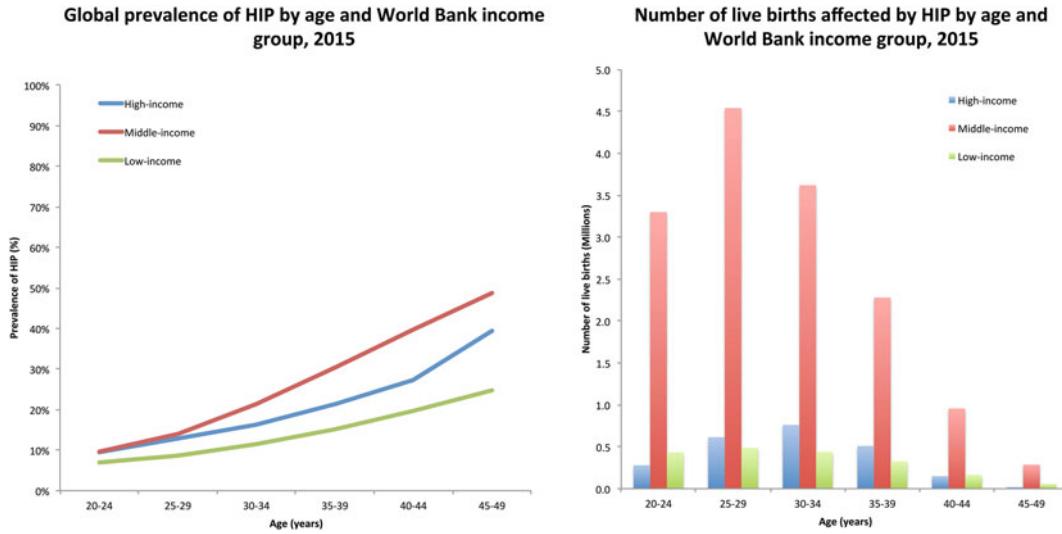


Fig. 1.5 Hyperglycaemia in pregnancy in women aged 20–49 years by income group region, 2015. *Data source* [37]

Conclusion: The Future of HIP and the Public Health Response

Quantifying the burden of HIP remains a challenge. Universal harmonisation of a definition for identification and categorisation remains to be achieved. In 2013 the WHO decided to accept the general principles behind how the IADPSG criteria were derived in the interest of moving towards a universal standard recommendation for the diagnosis of GDM. While this approach has been adopted by many national organisations, others continue to use different criteria [41].

Early identification through universal antenatal care and screening are the best chance for women and offspring to prevent the possible complications related to HIP, particularly in the most severe cases. However, a practical challenge is the reality that many developing countries and health systems around the world do not have the capacity to implement a GDM detection programme based on all or only high risk women having a 2-h OGTT and therefore options which do not involve an OGTT need to be considered [42, 43]. The other dilemma which faces health systems is maximising available country resources and prioritising and balancing resource between improving care of people with diabetes and finding and treating more people with undiagnosed diabetes, including GDM. Screening is not appropriate unless adequate care can be provided.

Trends in demographics, population growth and ageing, fertility, and diabetes are all projected to increase dramatically in the next generations. In combination with changes in lifestyle and risk factors contributing to overweight and obesity, these will lead to more and more cases of HIP. Identification, management and prevention of these cases will inevitably pose a heavy burden on the health system, particularly of developing countries where growth and change are happening at a rapid pace. For low-resource settings, priority will have to be on providing adequate antenatal care with counselling on healthy eating and physical activity. Health systems will have to be strengthened and health professionals should be educated to provide care integrated with antenatal services.

References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diab Res Clin Pract. 2014;103(2):137–149.
2. World Health Organization. WHO global report on diabetes [Internet]. Geneva, Switzerland; 2016 [cited 2016 Apr 13]. Available from: http://www.who.int/diabetes/global-report/en/.
3. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diab Res Clin Pract. 2014;103(2):176–185.
4. Group THSCR. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.
5. Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern Fetal Med. 2000;9(1):83–8.
6. Linnenkamp U, Guariguata L, Beagley J, Whiting DR, Cho NH. The IDF diabetes atlas methodology for estimating global prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103(2):186–196.
7. O'sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes. 1964;13:278–85.
8. WHO. Expert committee on diabetes mellitus: second report. WHO Tech Rep Ser. 1980;646:1–80.
9. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979;28(12):1039–57.
10. Ramos-Leví AM, Pérez-Ferre N, Fernández MD, Del Valle L, Bordiu E, Bedia AR, et al. Risk factors for gestational diabetes mellitus in a large population of women living in Spain: implications for preventative strategies. Int J Endocrinol. 2012;2012:1–9.
11. Yang H, Wei Y, Gao X, Xu X, Fan L, He J, et al. Risk factors for gestational diabetes mellitus in Chinese women—a prospective study of 16,286 pregnant women in China. Diabet Med. 2009;26(11):1099–104.
12. Cypryk K, Szymczak W, Czupryniak L, Sobczak M, Lewiński A. Gestational diabetes mellitus—an analysis of risk factors. Endokrynol Pol. 2008;59(5):393–7.
13. Shirazian N, Emdadi R, Mahboubi M, Motevallian A, Fazel-Sarjuei Z, Sedighpour N, et al. Screening for gestational diabetes: usefulness of clinical risk factors. Arch Gynecol Obstet. 2009;280(6):933–7.
14. Panel* IA of D and PSGC. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care. 2010;33(3):676–82.
15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diab Care. 2012;36 (Supplement_1):S67–74.
16. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Geneva, Switzerland;2013. Report no.: WHO/NMH/MND/13.2.
17. United Nations Department of Economics and Social Affairs, Population Division, Population Estimates and Projections Section. World Population Prospects: The 2012 Revision [Internet]. [cited 2013 Jun 14]. Available from: http://esa.un.org/wpp/.
18. United Nations. The world at six billion [internet]. New York, USA: United Nations Population Division; 1999. Available from: http://www.un.org/esa/population/publications/sixbillion/sixbillion.htm.
19. United Nations. World population prospects. 2015 Revision [Internet]. New York, USA: Population Division;2015. Available from: http://esa.un.org/unpd/wpp/.
20. Bongaarts J. Human population growth and the demographic transition. Philos Trans R Soc Lond B Biol Sci. 2009;364(1532):2985–90.
21. Montgomery K. The demographic transition [internet]. Wisconsin: University of Wisconsin; [cited 2016 Apr 13]. Available from: http://pages.uwc.edu/keith.montgomery/Demotrans/demtran.htm.
22. Myrskylä M, Kohler H-P, Billari FC. Advances in development reverse fertility declines. Nature. 2009;460 (7256):741–3.
23. Family Planning in China [Internet]. [cited 2016 Apr 13]. Available from: http://www.fmprc.gov.cn/ce/celt/eng/zt/zfbps/t125241.htm.
24. Alkema L, Kantorova V, Menozzi C, Biddlecom A. National, regional, and global rates and trends in contraceptive prevalence and unmet need for family planning between 1990 and 2015: a systematic and comprehensive analysis. The Lancet. 2013;381(9878):1642–52.
25. Alkema L, Raftery AE, Gerland P, Clark SJ, Pelletier F, Buettner T, et al. Probabilistic projections of the total fertility rate for all countries. Demography. 2011;48(3):815–39.
26. WHO Health Transition [Internet]. WHO. [cited 2016 Mar 23]. Available from: http://www.who.int/trade/glossary/story050/en/.
27. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. The Lancet. 2012;380(9859):2095–128.

28. Oggioni C, Lara J, Wells JCK, Soroka K, Siervo M. Shifts in population dietary patterns and physical inactivity as determinants of global trends in the prevalence of diabetes: an ecological analysis. Nutr Metab Cardiovasc Dis NMCD. 2014;24(10):1105–11.
29. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. Obes Rev Off J Int Assoc Study Obes. 2012;13(8):659–80.
30. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012;70(1):3–21.
31. Amuna P, Zotor FB. Epidemiological and nutrition transition in developing countries: impact on human health and development. Proc Nutr Soc. 2008;67(1):82–90.
32. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. The Lancet. 2012;380(9838):247–57.
33. Bao W, Tobias DK, Bowers K, et al. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus: a prospective cohort study. JAMA Intern Med. 2014;174(7):1047–55.
34. Freak-Poli R, Wolfe R, Peeters A. Risk of cardiovascular disease and diabetes in a working population with sedentary occupations. J Occup Environ Med Am Coll Occup Environ Med. 2010;52(11):1132–7.
35. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. Am J Clin Nutr. 2006;84(2):289–98.
36. Abou-Zahr CL, Wardlaw T. Antenatal care in developing countries—promises, achievements and missed opportunities: an analysis of trends, levels and differentials, 1990–2001 [Internet]. Geneva, Switzerland: World Health Organization;2003. Report No.: WQ 175 2003AN. Available from: http://www.who.int/maternal_child_adolescent/documents/9241590947/en/.
37. International Diabetes Federation. The international diabetes federation diabetes atlas, 7th ed. Brussels, Belgium;2015.
38. Chamberlain C, McNamara B, Williams ED, Yore D, Oldenburg B, Oats J, et al. Diabetes in pregnancy among indigenous women in Australia, Canada, New Zealand and the United States: a systematic review of the evidence for screening in early pregnancy. Diabetes Metab Res Rev. 2013;29(4):241–256.
39. Liu SL, Shah BR, Naqshbandi M, Tran V, Harris SB. Increased rates of adverse outcomes for gestational diabetes and pre-pregnancy diabetes in on-reserve first nations women in Ontario, Canada. Diabet Med J Br Diabet Assoc. 2012;29(8):e180–3.
40. International Diabetes Federation. International diabetes federation diabetes atlas, 6th ed. Brussels, Belgium;2013.
41. McIntyre HD, Colagiuri S, Roglic G, Hod M. Diagnosis of GDM: a suggested consensus. Best Pract Res Clin Obstet Gynaecol. 2015;29(2):194–205.
42. Colagiuri S, Falavigna M, Agarwal MM, Boulvain M, Coetzee E, Hod M, et al. Strategies for implementing the WHO diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Diab Res Clin Pract. 2014;103(3):364–72.
43. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Renzo GCD, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynecol Obstet. 2015;1(131):S173–211.

Chapter 2
Diagnosis of Gestational Diabetes

Donald R. Coustan

Key Points

- International agreement with regard to the diagnosis of gestational diabetes is currently lacking.
- The two-step screening approach, with diagnostic criteria based on the use of a 100 g, 3-h OGTT, which is currently in wide use in the US and many other countries, is based upon the prediction of future diabetes in the mother rather than upon pregnancy outcomes.
- The former WHO criteria, using a 75 g, 2-h OGTT, were simply the same as the criteria for diabetes and prediabetes in nonpregnant individuals, and were not specially derived for pregnancy.
- The 75 g, 2-h OGTT is universally utilized for the diagnosis of diabetes and prediabetes in nonpregnant individuals.
- The HAPO study described the relationships between each of the 3 values on the 75 g, 20-h OGTT and various components of diabetic fetopathy.
- The IADPSG recommendations for diagnosing gestational diabetes are primarily based on data from the HAPO study, and are the only set of criteria based on pregnancy outcomes.
- International adoption of the IADPSG recommendations remains controversial, but once accomplished will allow direct comparisons among populations of the prevalence of GDM as well as treatment efficacy, using common criteria based upon pregnancy outcomes.

Keywords Gestational diabetes · Diagnostic criteria · International Association of Diabetes in Pregnancy Study Groups (IADPSG) · World Health Organization (WHO) · American College of Obstetricians and Gynecologists (ACOG) · American Diabetes Association (ADA) · The National Institute for Health and Care Excellence (NICE) · Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study · National Diabetes Data Group (NDDG) · International Federation of Gynecology and Obstetrics (FIGO)

Abbreviations

OGTT Oral glucose tolerance test
GDM Gestational diabetes mellitus

D.R. Coustan (✉)
Warren Alpert Medical School of Brown University, Providence, USA
e-mail: dcoustan@wihri.org

D.R. Coustan
Attending Maternal-Fetal Medicine Specialist, Women & Infants Hospital of Rhode Island,
101 Dudley Street, Providence, RI 02905-2401, USA

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_2

Introduction

Global estimates of the prevalence of diabetes in pregnancy [1], with the vast majority being gestational diabetes, average 16.9%, with the highest rate in Southeast Asia (25%) and the lowest rates in North America (10.4%). These estimates are handicapped by disparities in screening rates and in diagnostic criteria. There have been multiple schemes recommended for diagnosing gestational diabetes throughout the world, with glucose challenge doses of 50, 75, 100 g, and weight-based formulas and with varying diagnostic criteria. Table 2.1 lists some of the more commonly used approaches. The panoply of tests and criteria makes comparison of prevalence of gestational diabetes across populations virtually impossible. We shall describe some of the more commonly used criteria and put each into perspective.

Development of the O'Sullivan and Mahan Criteria and Various Conversions

Gestational diabetes was described in 1882, although not named, by J. Matthews Duncan, who stated, "Diabetes may come on during pregnancy…diabetes may occur only during pregnancy…diabetes may cease with the termination of pregnancy…" [2]. Elsie Reed Carrington was the first to use the term "gestational diabetes" in 1957 [3]. Until the mid-1960s, the criteria most commonly used in the United States for diagnosing diabetes in pregnancy were those of the US Public Health Service, which required, in a 100 g, 3-h oral glucose tolerance test (OGTT) that both the fasting and 3-h values meet or exceed 7.2 mmol/L (130 mg/dL), or else one of the above two values exceed threshold and both the 1-h value meet or exceed 10.8 mmol/L (195 mg/dL) and the 2-h value exceed 7.8 mmol/L (140 mg/dL). These were the same criteria used in the nonpregnant state. In 1964, O'Sullivan and Mahan [4] observed that pregnancy changes carbohydrate metabolism such that glucose tolerance may be altered. Pointing out that nonpregnant norms may not be valid, they reported the results of

Table 2.1 Various diagnostic criteria for gestational diabetes mellitus (GDM)

	NDDG[a]	C & C[b]	WHO[c]	ADIPS[d]	CDA[e]	IADPSG[f]
# elevated values	2	2	1 + nl fasting	1	1	1
Glucose challenge	100 g	100 g	75 g	75 g	75 g	75 g
Fasting threshold mmol/L (mg/dL)	5.8 (105)	5.3 (95)	Nl < 7.0 (<126)	5.5 (99)	5.3 (95)	5.1 (92)
1-hr mmol/L (mg/dL)	10.8 (190)	10.0 (180)	NA	NA	10.6 (191)	10.0 (180)
2-hrs mmol/L (mg/dL)	9.2 (165)	8.6 (155)	7.8–11.1 (140–200)	8.0 (144)	9.0 (162)	8.5 (153)
3-hrs mmol/L (mg/dL)	8.0 (145)	7.8 (140)	NA	NA	NA	NA

[a]National Diabetes Data Group [5] conversion of O'Sullivan and Mahan criteria [4]; two or more elevated values needed to diagnose gestational diabetes

[b]Carpenter and Coustan [6] conversion of O'Sullivan and Mahan criteria [4]; two or more elevated values needed to diagnose gestational diabetes

[c]World Health Organization criteria [8]. Fasting plasma glucose must be normal and 2-h value elevated. If fasting is >7.0 or 2-hr > 11.1 diabetes mellitus is diagnosed. WHO adopted IADPSG criteria in 2013 [36]

[d]Australasian Diabetes in Pregnancy Society (ADIPS) criteria [44]; GDM is diagnosed if either the fasting and/or 2-h value is elevated. ADIPS adopted the IADPSG criteria in 2013–2014 [45]

[e]Canadian Diabetes Association criteria [46]. One or more elevated value diagnoses gestational diabetes. The IADPSG approach is considered an alternative, though not preferred

[f]International Association of Diabetes in Pregnancy Study Groups criteria [13]; one or more elevated values diagnoses gestational diabetes

100 g, 3-h OGTTs on 752 unselected pregnant women tested primarily in the late second and early third trimesters. Glucose was measured in venous whole blood samples, using the Somogyi–Nelson method of analysis. The investigators derived potential thresholds at 1, 2, and 3 standard deviations above the means for each of the four samples. The potential thresholds were then applied retrospectively to a second data set of OGTTs during pregnancy among 1333 women who had subsequently undergone periodic OGTTs in the nonpregnant state. Cutoffs of two standard deviations above the mean yielded a prevalence of GDM of 1.9%. It was determined that 22% of women whose pregnancy OGTTs met these thresholds developed diabetes within 8 years after pregnancy. The investigators explained that using cutoffs of one standard deviation would have labeled 16% of pregnant women with GDM, compared to a prevalence of diabetes in the nonpregnant community of 2%. They required that at least two of the four thresholds be met or exceeded, stating, "It was considered expedient…to require two or more values to be met or exceeded. In this way misclassification due to a laboratory error, or occasional single high peaks resulting from unusually rapid absorption of glucose, could be avoided." The four cutoffs were then rounded off to the nearest 5 mg/dL for ease of remembering. These diagnostic criteria are depicted in Table 2.2.

While glucose was typically measured in whole blood when O'Sullivan and Mahan performed their study, plasma and serum samples subsequently became routine. When whole blood glucose is analyzed the red cells continue to metabolize glucose until measurement is carried out, leading to potential spuriously low values. By separating the red cells from plasma by centrifugation, or allowing the blood to clot and then decanting the serum, this problem can be potentially avoided (depending upon the time elapsing between blood draw and separation). However, when whole blood glucose is measured, the red cells make up some of the volume (denominator of the fraction) but do not contribute to the glucose measurement (numerator). Thus, whole blood glucose is lower than plasma or serum glucose measured simultaneously. In 1979, the National Diabetes Data Group [5] published a conversion of the O'Sullivan cutoffs by adding 15% to each of the already rounded thresholds, then rounding again to the nearest 5 mg/dL (see Table 2.3).

The NDDG conversion of the O'Sullivan and Mahan criteria was widely accepted in the United States. However, in 1982 [6] Carpenter and Coustan noted that the methodology for glucose measurement had been updated from the Somogyi–Nelson method, which measured about 5 mg/dL of reducing substances other than glucose, to enzymatic methods such as glucose oxidase or hexokinase, which measured only glucose. They converted the O'Sullivan and Mahan criteria to enzymatic methods by subtracting 5 mg/dL from each of the original unrounded cutoffs, then adding 14% to the resulting value which is a more accurate conversion from whole blood to plasma than the 15% used by the NDDG. These converted criteria for plasma or serum, using enzymatic methodologies, are shown in Table 2.4. The two conversions from the original O'Sullivan and Mahan criteria were compared by recreating the original methodology (whole blood, Somogyi–Nelson) and analyzing the same samples using plasma and enzymatic methodology [7]. The NDDG criteria were found to be within 95% confidence limits of

Table 2.2 O'Sullivan and Mahan OGTT criteria to diagnose GDM, both unrounded and rounded to the nearest 5 mg/dL (0.27 mmol/L) [4]

	Unrounded	Rounded
Fasting	90 mg/dL (5 mmol/L)	90 mg/dL (5 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	165 mg/dL (9.2 mmol/L)
2 h	143 mg/dL (7.9 mmol/L)	145 mg/dL (8.0 mmol/L)
3 h	127 mg/dL (7.1 mmol/L)	125 mg/dL (6.9 mmol/L)

Venous whole blood, Somogyi–Nelson method of analysis
Two or more elevated values required for the diagnosis of GDM

Table 2.3 NDDG [5] conversions of the original O'Sullivan and Mahan [4] cutoffs

	Venous whole blood	Venous plasma
Fasting	90 mg/dL (5 mmol/L)	105 mg/dL (5.8 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	190 mg/dL (10.6 mmol/L)
2 h	145 mg/dL (8.0 mmol/L)	165 mg/dL (9.2 mmol/L)
3 h	125 mg/dL (6.9 mmol/L)	145 mg/dL (7.9 mmol/L)

Two or more elevated values required for the diagnosis of GDM

Table 2.4 Carpenter and Coustan [6] conversions of original O'Sullivan and Mahan [4] criteria

	Venous whole blood[a]	Venous plasma[b]
Fasting	90 mg/dL (5 mmol/L)	95 mg/dL (5.3 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	180 mg/dL (10.0 mmol/L)
2 h	143 mg/dL (7.9 mmol/L)	155 mg/dL (8.6 mmol/L)
3 h	127 mg/dL (7.1 mmol/L)	140 mg/dL (7.8 mmol/L)

[a]Somogyi–Nelson methodology
[b]Glucose oxidase or hexokinase methodology
Two or more elevated values required for the diagnosis of gestational diabetes

the original O'Sullivan and Mahan methodology only for the fasting value; the other three were above the upper limits. The Carpenter and Coustan conversion were within 95% confidence limits for all samples. Both conversions are utilized in various settings in the United States.

The World Health Organization (WHO) Criteria

Since 1998 [8], the WHO recommended the use of criteria for GDM which were the same as those used for impaired glucose tolerance and diabetes in nonpregnant individuals (Table 2.1). These were not derived specifically for particularly for pregnancy. In 2013 the WHO adopted the IADPSG criteria (see below).

Development of the IADPSG Criteria

As early as 1991, the Third International Workshop Conference on Gestational Diabetes Mellitus (Metzger et al. 1991) concluded that the use of a variety of glucose challenges, and a variety of diagnostic criteria, made it impossible to compare prevalences of GDM across populations. Results of intervention studies were difficult to generalize. None of the available criteria were based on pregnancy outcomes. Furthermore, it was pointed out that the 75 g OGTT was universally accepted for nonpregnant individuals, and it was assumed that the same challenge would eventually become the standard for pregnancy. A 1992 NICHD sponsored International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes [9] concluded, "…questions about…efforts to diagnose and treat GDM to prevent adverse perinatal effects cannot be resolved without additional carefully designed studies. [HAPO]…will enable the investigators to correlate various degrees of glucose intolerance with perinatal morbidity…".

The above events led to the initiation of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, which was designed to determine what level of glucose intolerance during pregnancy,

short of diabetes, is associated with an increased risk of adverse outcomes [10]. HAPO was a purely observational, noninterventional study with participation from 15 field centers in nine different countries around the globe. Over 23,000 pregnant women completed the study, in which a 75 g, 2-h OGTT was administered at 24–32 weeks gestation (mean 27.8 ±1.8 weeks). The results were masked from subjects and their providers unless the 2-h value met or exceeded 11.1 mmol/L (200 mg/L) or the fasting value exceeded 5.8 mmol/L (105 mg/dL). Maternal and neonatal outcomes were recorded. Recruitment encompassed 6 years, from 2000 to 2006. Each of the four primary outcomes (birthweight >90th centile, primary cesarean section, neonatal hypoglycemia and cord C-peptide >90th centile [a proxy for fetal insulin]) was correlated to each of the three plasma glucose levels in a continuous fashion, without any inflection point (Fig. 2.1). These relationships held even when adjusted for such potential confounders as field center (a proxy for ethnicity and geographical location), maternal age, maternal BMI, and gestational age at the time of the OGTT, among others. A number of prespecified secondary outcomes (preeclampsia, shoulder dystocia/birth injury, premature delivery, and neonatal adiposity [11]) were similarly associated with GTT values in a linear and statistically significant fashion. These relationships were highly supportive of the "Pedersen Hypothesis," namely that maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal hyperinsulinemia which is the primary cause of diabetic fetopathy [12], in that cord blood C-peptide was directly related to both OGTT glucose values and to neonatal macrosomia and adiposity.

Because there were no obvious inflection points in the HAPO data, the HAPO investigators understood that any recommendations for diagnosing gestational diabetes would be relatively arbitrary, and they decided not to recommend specific cutoffs lest the criteria become known as "HAPO criteria" and attaining international agreement would be more difficult. Since the only way to determine appropriate diagnostic criteria would be to consult a group of experts the International Association of Diabetes in Pregnancy Study Groups (IADPSG) convened 225 conferees from 40 different countries around the world in 2008. They considered the HAPO data as well as data from other available published studies. An IADPSG consensus panel was convened, and spent over a year considering the data and potential recommendations. It was decided to use large babies, primary cesarean sections and cord blood C-peptide above the 90th centile as the outcomes to be utilized for developing cutoffs for GDM, with the knowledge that any of the other adverse outcome variables could have as well be used because of the similarity of the relationships between OGTT glucose values and each of the primary and secondary outcomes. It was decided to use mean OGTT glucose values for comparison, and odds ratios for the above three outcomes were calculated for various levels of OGTT glucose above mean levels. The consensus was to use odds ratios of 1.75, and to diagnose GDM based on one or more glucose values above threshold, since the three OGTT values each independently identified individuals with elevated risk. These cutoffs would identify 16.1% of the HAPO population as having GDM, along with an additional 1.7% of subjects who were unblinded because their GTT values or random glucose values were a priori considered to require identification and treatment, bringing the grand total of GDM to 17.8% of the HAPO population. The recommended thresholds are shown in Table 2.5, and were published in 2010 [13].

Various critics have suggested that the IADPSG consensus group should have chosen an odds ratio of 2.0 rather than 1.75, on the assumption that a 1.75 odds ratio identified women with an approximately 75% increase in the likelihood of adverse outcomes, and a doubling would have been more reasonable [14, 15]. In fact, while the 1.75 odds ratio compares individuals with GDM to those whose plasma glucose levels all are at the population mean, a more appropriate comparison would be between those with GDM and all those in the population without GDM. Such a comparison is depicted in Table 2.6, which demonstrates that those with GDM have at least twice the likelihood of large babies, fat babies, hyperinsulinemic babies and preeclampsia, and a one-third greater likelihood of preterm birth, primary cesarean section, and shoulder dystocia.

The major drawback to adopting the IADPSG recommendations for diagnosing gestational diabetes seems to have been the fact that such a high proportion of pregnant women would be considered

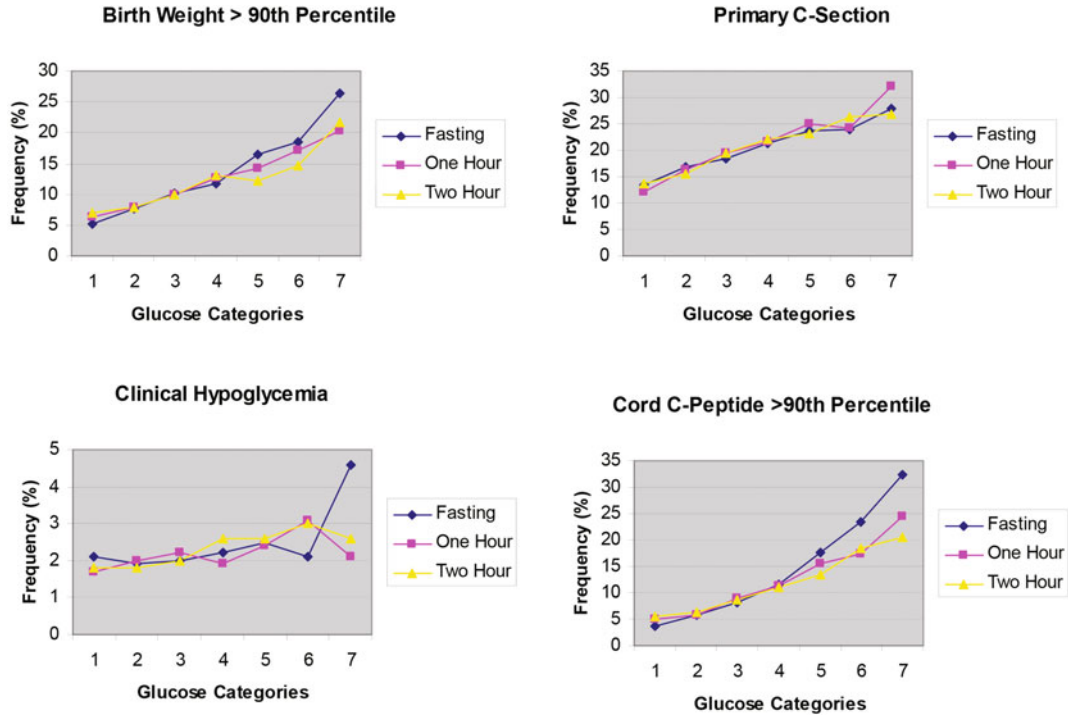


Fig. 2.1 Associations between each of the three GTT plasma glucose levels and each of the four primary outcomes in the HAPO study. Relationship of each of the three 75 g, 2-h OGTT values to each of the four primary outcomes in the HAPO study. (Reprinted with permission from New England Journal of Medicine. HAPO Study Cooperative Research Group [10]. Reprinted with permission). Copyright © 2008 Massachusetts Medical Society. *Legend* Glucose categories are defined as follows: fasting plasma glucose level—category 1, less than 75 mg per deciliter (4.2 mmol/L); category 2, 75–79 mg/dL (4.2–4.4 mmol/L); category 3, 80–84 mg/dL (4.5–4.7 mmol/L); category 4, 85–89 mg/dL (4.8–4.9 mmol/L); category 5, 90–94 mg/dL (5.0–5.2 mmol/L); category 6, 95–99 mg/dL (5.3–5.5 mmol/L); category 7, 100 mg/dL (5.6 mmol/L) or more. 1-h plasma glucose level—category 1, 105 mg/dL (5.8 mmol/L) or less; category 2, 106–132 mg/dL (5.9–7.3 mmol/L); category 3, 133–155 mg/dL (7.4–8.6 mmol/L); category 4, 156–171 mg/dL (8.7–9.5 mmol/L); category 5, 172–193 mg/dL (9.6–10.7 mmol/L); category 6, 194–211 mg/dL (10.8–11.7 mmol/L); category 7, 212 mg/dL (11.8 mmol/L) or more. 2-hr plasma glucose level—category 1, 90 mg/dL (5.0 mmol/L) or less; category 2, 91–108 mg/dL (5.1–6.0 mmol/L); category 3, 109–125 mg/dL (6.1–6.9 mmol/L); category 4, 126–139 mg/dL (7.0–7.7 mmol/L); category 5, 140–157 mg/dL (7.8–8.7 mmol/L); category 6, 158–177 mg/dL (8.8–9.8 mmol/L); category 7, 178 mg/dL (9.9 mmol/L) or more

Table 2.5 IADPSG recommended thresholds for diagnosing gestational diabetes mellitus (IADPSG, 2008)

Fasting plasma glucose	1-h plasma glucose	2-h plasma glucose
5.1 mol/L (92 mg/dL)	10 mmol/L (180 mg/dL)	8.5 mmol/L (153 mg/dL)

Gestational diabetes is diagnosed if one or more of the above values is met or exceeded

to have GDM, and diagnosing 16–18% with this condition would place an undue burden on patients and the healthcare system [16]. It should be noted, however, that recent data from the National Health and Nutrition Examination Survey (NHANES) [17] show that, depending upon the diagnostic tests utilized, 12.2–14.3% of Americans aged 20 years or more had diabetes in 2011–2012; worldwide estimates are that this disease affects 9% of individuals aged 18 or more years [18]. The prevalence of prediabetes in the United States, among individuals aged 20 years or more, was 36.5–38% in 2011–2012 [17], meaning that at least 52% of American adults now have prediabetes or diabetes! The prevalence of diabetes in those aged 20–44 years, roughly the childbearing years, was 4.5–5.0% and

Table 2.6 Outcomes of untreated subjects with gestational diabetes, using new IADPSG criteria (data from online appendix, Table B, IADPSG [13]

Outcome	All values < threshold (No. GDM) (%)	Any ≥ 92/180/153 gestational diabetes
Birthweight >90th percentile	8.3	16.2%@
Cord C-peptide >90th percentile	6.7	17.5%@
% Body fat >90th percentile	8.5	16.6%@
Preeclampsia	4.5	9.1%@
Preterm birth (<37 weeks)	6.4	9.4%@
Shoulder dystocia/birth injury	1.3	1.8%*
Primary cesarean section	16.8	24.4%@

*$p < 0.01$; @$p < 0.001$

of prediabetes 25.1–28.2%, meaning that 29–33% of Americans in the childbearing age range had disordered glucose metabolism. The IADPSG criteria for GDM resemble the criteria for prediabetes [impaired fasting glucose is 5.6–6.9 mmol/L (100–124 mg/dL) and impaired glucose tolerance is 7.8–11 mmol/L (140–199 mg/dL) at 2-h of the 75 g OGTT in nonpregnant individuals]. It should not be surprising that 18% of pregnant women have gestational diabetes. The criteria for diabetes and prediabetes in nonpregnant adults are similar if not the same throughout the world. The response to the epidemic of diabetes and prediabetes has not been to redefine these disorders in order to relieve the burden on healthcare systems. Instead, innovative approaches to providing cost-effective, evidence-based health care are being developed globally. This is the challenge for dealing with the increasing number of women with GDM. Potential targets for cost savings without adverse consequences include the use of group prenatal/diabetes visits [19], and the exploration of the practicality and safety of decreasing the frequency of blood glucose testing and fetal testing in women with milder forms of gestational diabetes [20].

Another concern that has been raised is whether it would be cost-effective to diagnose and treat GDM in so many pregnant women [16]. Mission et al. [21] performed a decision analysis comparing the two-step process ACOG [22] with the IADPSG one-step process and determined that the one-step process was more expensive, but more effective and more cost-effective. In another comparison, Werner et al. [23] reported that the IADPSG approach is more cost-effective as long as the women with GDM receive postdelivery counseling and care aimed at preventing type 2 diabetes. In the above analysis, the authors assumed that the rate of GDM would be 3.8% with the 2-step approach and 16.2% with the IADPSG approach. In fact, statewide reported rates of GDM in the United States ranged from 3.5 to 7% in 2008 [24], prior to publication of the IADPSG recommendations in 2010, so the 3.8% estimate of the GDM rate with the two-step approach is an underestimate; assuming a higher baseline rate of GDM would presumably make the adoption of the IADPSG recommendations even more cost-effective. This discussion raises the question of whether interventions after delivery can prevent type 2 diabetes in women with previous GDM. In a subgroup analysis of subjects with previous GDM and prediabetes who were enrolled in the Diabetes Prevention Program, Ratner et al. [25] demonstrated that the annual rate of conversion to type 2 diabetes was reduced by 50% in the group receiving metformin and the group receiving intensive lifestyle intervention compared to those randomized to placebo. The number needed to treat to prevent one conversion to type 2 diabetes over three years was 5 with lifestyle intervention and 6 with metformin.

Another question that has been raised is whether identification and treatment of milder forms of GDM, using the IADPSG recommendations, would be beneficial. While no randomized controlled trials (RCTs) of identification and treatment of GDM using the IADPSG recommendations have been published, there have been two RCTs of identification and treatment of mild forms of GDM using

other criteria. The NICHD Maternal-Fetal Medicine Units (MFMU) Network [26] randomized patients whose 3-h, 100 g OGTTs met the Carpenter and Coustan conversion of the O'Sullivan criteria, but had normal fasting plasma glucose levels (<5.3 mmol/L or 95 mg/dL) to identification and treatment (N = 485) or routine care (N = 473). Caregivers and subjects randomized to routine care were masked to the OGTT values. Identification and treatment of mild GDM decreased fetal macrosomia, preeclampsia and shoulder dystocia by more than 50%. The ACHOIS study [27] similarly randomized patients whose GDM (plasma glucose 2 h after a 75 g glucose challenge of 7.8–11.0 mmol/L or 140–199 mg/dL; mean fasting value 4.8 mmol/L or 86 mg/dL) was even milder than those who would be identified by the IADPSG recommendations [2 h value of 8.5 mmol/L or greater (153 mg/dL or greater)]. Those whose mild GDM was identified and treated were 2/3 less likely to experience a composite of perinatal death, shoulder dystocia, bone fracture, or nerve palsy than those randomized to routine treatment (and blinded to the OGTT results). Furthermore, macrosomia was half as likely and preeclampsia was 33% less likely. Since the subjects in this RCT had milder OGTT results than those recommended by IADPSG, it is reasonable to extrapolate that identification and treatment of GDM using the IADPSG recommendations will lower rates of adverse outcomes.

Because the 75 g, 2-h OGTT is known to be an unstable test, critics of the IADPSG one-step approach have argued that there is an increased risk of false positive results when only a single test is used and a single elevated value diagnoses GDM [16]. The one-step, 75 g 2-h OGTT is universally accepted worldwide for diagnosing diabetes in nonpregnant individuals, and there is no reason to believe that pregnancy renders the test more unstable or less reliable. It has also been argued that patient acceptance will be lower with the requirement to fast and wait 2 h for the test to be completed than with the two-step process in which fasting is not required and a 1-h wait is needed for the first step. When Sacks et al. [28] offered the choice of the one-step 75 g, 2-h OGTT versus the traditional two-step test to 4078 gravidas, 3505 (86%) chose the one-step approach. These findings suggest that patient acceptance is unlikely to be a major problem.

The biggest difference between the modified O'Sullivan criteria and the IADPSG criteria is the requirement for only one, rather than two elevated values to diagnose GDM. The rationale for requiring two elevated values was as follows [4]: "It was considered expedient…to require two or more values to be met or exceeded. In this way misclassification due to a laboratory error, or occasional single high peaks resulting from unusually rapid absorption of glucose, could be avoided." Laboratory errors, while still possible, are much less likely in the present era of bar codes and universal precautions. Because the HAPO data [10] showed that each of the three OGTT values was independently predictive of adverse outcomes, and the IADPSG cutoffs for the three values were each based on a similar predictive value, one or more elevations now diagnose GDM.

Early Pregnancy Testing for Preexisting Diabetes

One of the major issues confronting the IADPSG consensus panel was the identification of preexisting diabetes first diagnosed during pregnancy. As the prevalence of type 2 diabetes has reached epidemic proportions globally, there is an increasing likelihood that women will enter pregnancy with previously undiagnosed diabetes. Older definitions of gestational diabetes included any diabetes first diagnosed during pregnancy that subsequently disappeared postpartum, but of course one could not know the postpartum course until after completion of pregnancy. In the extreme, even a patient presenting in diabetic ketoacidosis in the first trimester would, strictly speaking, be labeled as having "gestational diabetes" until her type 1 diabetes could be found to remain after delivery. Thus, there was a need to develop criteria for the diagnosis of preexisting diabetes in early pregnancy. IADPSG [13] recommendations are that any of the standard definitions of diabetes outside of pregnancy, including fasting plasma glucose $\geq$7 mmol/L (126 mg/dL), A1c $\geq$6.5% or random plasma

glucose $\geq$11.1 mmol/L (200 mg/dL) when confirmed would diagnose preexisting diabetes in early pregnancy. One of the problems with the IADPSG guidelines is that if the fasting plasma glucose in early pregnancy is <7 mmol/L (126 mg/dL) but $\geq$5.1 mmol/L (92 mg/dL) the recommendation was to diagnose GDM. The IADPSG GDM criteria were based on OGTT data from 24 to 32 weeks, and there is no evidence for or against their validity in early pregnancy. Another problem is that there is no certainty as to when in pregnancy the usual criteria for diagnosing diabetes in the nonpregnant state are no longer valid. A1c levels fall during pregnancy [29, 30] and may under diagnose preexisting diabetes, while the hyperglycemia associated with GDM may raise A1c. Similarly, as pregnancy progresses it may be difficult to distinguish preexisting diabetes from GDM based on a random plasma glucose above 11.1 mmol/L.

The National Institute for Health and Care Excellence (NICE) Guidelines

In 2015, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published evidence-based recommendations for diagnosing GDM [31]. Risk factor screening is advised at the first prenatal visit. Gravidas with BMI >30, previous baby weighing 4.5 kg or more, previous GDM, diabetes in a first-degree relative, a minority ethnic family origin with a high prevalence of diabetes, or glycosuria of 1+ on 2 or more occasions or 2+ on one occasion are offered a 75 g, 2-h OGTT at 24–28 weeks. Those with previous GDM are offered earlier testing or self-glucose monitoring. GDM is diagnosed if the fasting plasma glucose is 5.6 mmol/L (101 mg/dL) or above or the 2-h value is 7.8 mmol/L (140 mg/dL) or above. The fasting plasma glucose cutoff is higher than the IADPSG recommendation of 5.1 mmol/L (92 mg/dL) and the 2-h cutoff is lower than the 8.5 mmol/L (153 mg/dL) recommended by IADPSG.

In a retrospective review of over 25,000 pregnancies in which 75 g, 2-h OGTTs were performed in 3848 women (based on risk factors), 387 had GDM by IADPSG cutoffs but not by NICE cutoffs [32], whereas 1055 had GDM by NICE criteria (794 of whom also met IADPSG criteria). The vast majority of patients with GDM by NICE criteria were offered treatment while none of those meeting only the IADPSG criteria were treated. The untreated women meeting only IADPSG cutoffs delivered more babies with birthweight >90th percentile than those without GDM (30 vs. 17%), and more than treated GDMs meeting only the NICE cutoffs (11.5%). Untreated women with fasting plasma glucose between the IADPSG cutoff (5.1 mmol/L or 92 mg/dL) and the NICE cutoff (5.5 mmol/L or 101 mg/dL) had the highest proportion of LGA infants (38%). The prevalence of GDM in this primarily Caucasian population was 4.1% with the NICE criteria and 4.6% with the IADPSG criteria, although GTTs were only performed in women whose 50 g, 1-hr screening test was >7.7 mmol/L (43 mg/dL) so GDM may have been under-identified.

The NICE guidelines lower the 2-h cutoff by 0.7 mmol/L (13 mg/dL), raise the fasting cutoff by 0.5 mol/L (9 mg/dL) and reject the 1-h value of the IADPSG criteria. Each of the three IADPSG cutoffs are similarly associated with adverse outcomes, and are independent enough that omitting the 1-h test would have missed 26 and 30% of the GDMs diagnosed in the subjects at the two UK HAPO centers [33]. It is unfortunate that these diagnostic threshold recommendations, which are not so different from IADPSG, could not coincide. Another important difference is that the NICE recommendations are, in essence, a two-step process with the first step being screening by history. There is plentiful evidence that screening by risk factors is quite insensitive [34]. For example, a history of a large baby or previous GDM means that women having their first pregnancy cannot possibly demonstrate those factors. It is as if we are willing to allow the adverse outcome to occur in the first pregnancy, and then try to prevent it in future pregnancies.

Current Recommendations Around the World

The IADPSG recommendations [13] were developed with the intention to produce guidelines and criteria for diagnosing gestational diabetes, which were based on evidence regarding pregnancy outcomes and were agreed upon by a consensus of experts from around the world, and would be adopted globally. Such worldwide agreement would remove confusion about definitions of GDM, allow comparisons among diverse populations with regard to prevalence and also with regard to treatment efficacy. As might be anticipated from examples such as UN deliberations on war and peace, and evolving attitudes toward climate change, reaching such agreement is arduous and time-consuming. However, a good deal of progress has been made since the recommendations were published, and this section of the chapter will describe the state of affairs as of the spring of 2016.

In the United States a consensus conference held in 2013 [16] recommended continuing the use of the two-step approach with either set of conversions of diagnostic criteria based on the O'Sullivan and Mahan 100 g, 3-h OGTT. The one-step IADPSG approach could be considered once further evidence of benefit has accumulated. The American College of Obstetricians and Gynecologists [22] makes similar recommendations. The American Diabetes Association [35] recommends either the ACOG two-step approach or the IADPSG one-step approach, and emphasizes the stronger evidence behind the IADPSG approach.

In 2013, the World Health Organization [36] adopted the IADPSG recommendations for diagnosing gestational diabetes, and for diagnosing preexisting diabetes during pregnancy, adding the opportunity for flexibility depending upon the availability of healthcare resources. In 2015, the International Federation of Gynecology and Obstetrics (FIGO) also adopted the IADPSG recommendations [37] with room for flexibility depending upon the availability of healthcare resources.

Conclusions

Currently, the IADPSG recommendations are being implemented in a somewhat piecemeal fashion, in various parts of the world. Retrospective data have demonstrated that patients with unidentified, untreated GDM by IADPSG criteria are more likely to deliver macrosomic and LGA babies, and to experience cesarean delivery, than those with normal glucose tolerance [38]. While data from the US and Canada comparing hospital-wide pregnancy outcomes before and after the switch from Carpenter and Coustan criteria to IADPSG criteria failed to demonstrate an improvement in overall outcomes [39, 40] despite increases in the rate of identified and treated GDM, publications from Spain [41] Taiwan [42] and China [43] reported hospital-wide improvements in perinatal outcomes (cesarean sections in all three reports, large babies in China and Spain, hypertensive disorders of pregnancy in Spain, and a composite outcome of large babies, neonatal jaundice, NICU admissions and birth trauma in Taiwan) and overall cost savings in Spain. It remains to be seen when, if ever, we reach the goal of one glucose challenge dose and one set of diagnostic criteria in use throughout the world.

References

1. Guariguata L, Linnenkamp U, Baegley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy for 2013 for the IDF diabetes atlas. Diab Res Clin Pract. 2014;103:137–49.
2. Duncan JM. On puerperal diabetes. Trans Obstet Soc Lond. 1882;24:256–85.
3. Carrington ER, Shuman CR, Reardon HS. Evaluation of the prediabetic state during pregnancy. Obtet Gynecol. 1957;9:664–9.
4. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes. 1964;13:278–85.

5. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979;28:1039–57.
6. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144:768–73.
7. Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? Am J Obstet Gynecol. 1989;161:638–41.
8. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diab Med. 1998;15:539–53.
9. Blank A, Grave GD, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed: report of the international workshop on adverse perinatal outcomes of GDM. Diab Care. 1995;18:127–30.
10. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002.
11. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations with neonatal anthropometrics. Diabetes. 2009;58:453–9.
12. Pedersen J. Diabetes and pregnancy: blood sugar of newborn infants. Ph.D Thesis. Copenhagen: Danish Science Press; 1952.
13. International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care 2010;33:676–682.
14. Ryan EA. Diagnosing gestational diabetes. Diabetologia. 2011;54:480–6.
15. Long H, Cundy T. Establishing consensus in the diagnosis of gestational diabetes following HAPO: where do we stand? Curr Diab Rep. 2013;13:43–50.
16. National Institutes of Health Consensus Development Conference Statement. Diagnosing gestational diabetes mellitus. Obstet Gynecol. 2013;122:358–69.
17. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. JAMA. 2015;314:1021–9.
18. World Health Organization. Diabetes fact sheet number 312 January 2015. http://www.who.int/mediacentre/factsheets/fs312/en/. Accessed 29 Feb 16.
19. Mazzoni SE, Hill PK, Webster KW, Heinrichs GA, Hoffman MC. Group prenatal care for women with gestational diabetes. J Matern Fetal Neonatal Med. 2015;23:1–5.
20. Mendez-Figueroa H, Daley J, Lopes VV, Coustan DR. Comparing daily versus less frequent blood glucose monitoring in patients with mild gestational diabetes. J Matern Fetal Neonatal Med. 2013;26:1268–72.
21. Mission JF, Ohno MS, Cheng YW, Caughey AB. Gestational diabetes screening with the new IDPSG guidelines: a cost-effectiveness analysis. Am J Obstet Gynecol. 2012;207:326e1–9.
22. American College of Obstetricians and Gynecologists (ACOG). Gestational diabetes mellitus. Practice bulletin no. 137. Obstet Gynecol. 2013;122:406–16.
23. Werner EF, Pettker CM, Zuckerwise L, Reel M, Funai E, Henderson J, Thung S. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? Diab Care. 2012;35:529–35.
24. Bardenheier BH, Elixhauser A, Imperatore G, Devlin HM, Kuklina EV, Geiss LS, Correa A. Variation in prevalence of gestational diabetes mellitus among hospital discharges for obstetric delivery across 23 states in the United States. Diab Care. 2013;35:1209–14.
25. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE, The Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. JCEM. 2008;93:4774–9.
26. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. NEJM. 2009;361:1339–48.
27. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, and Robinson JS for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. NEJM. 2005;352:2477–86.
28. Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JFF. Toward universal criteria for gestational diabetes. Am J Obstet Gynecol. 1995;172:607–14.
29. Nielsen LR, Ekbom P, Damm P, Glümer C, Frandsen MM, Jensen DM, Mathiesen ER. HbA1c levels are significantly lower in early and late pregnancy. Diab Care. 2004;27:1200–1.
30. Mosca A, Paleari R, Dalfra MG, DiCianni G, Cuccuru A, Pellegrini G, Malloggi L, Bonomo M, Granata S, Cariotti F, Castiglioni MT, Songini M, Tocco G, Masin M, Plebani M, Lapolla A. Reference intervals for hemoglobin A1c in pregnant women: data from an Italian multicenter study. Clin Chem. 2006;52:1138043.

31. National Institute for Health and Care Excellence. Nice guidance: diabetes in pregnancy: management from preconception to the postnatal period. February 2016. http://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2. Accessed 6 Mar 2016.
32. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes mellitus: falling through the net. Diabetologia. 2015;58:2003–12.
33. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJN, Persson B, Trimble ER, for the HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. Diab Care. 2012;35:526–8.
34. Östlund A, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. Acta Obstet Gynecol Scand. 2003;82:103–8.
35. American Diabetes Association. Standards of care. Diab Care. 2016;39(Suppl 1):S18–20.
36. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Published in 2013. http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/. Accessed 14 Feb 16.
37. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, Cabero Roura L, McIntyre HD, Morris JL, Divakar H. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynecol Obstet. 2015;131:S173–211.
38. Ethridge JK Jr, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the International Association of the Diabetes and Pregnancy Study Groups Criteria. Obstet Gynecol. 2014;124:571–8.
39. Feldman RK, Tieu RS, Yasumara L. Gestational diabetes screening: the IADPSG compared with the C&C screening. Obstet Gynecol. 2016;127:10–7.
40. Kong JM, Lim K, Thompson DM. Evaluation of the International Association of the Diabetes in Pregnancy Study Group new criteria: gestational diabetes project. Can J Diab. 2015;39:128–32.
41. Duran A, Sáenz S, Torrejón MJ, Bordiú E, del Vzlle L, Galindo M, Perez N, Herraiz MA, Izquierdo N, Rubio MA, Runkle I, Pérez-Ferre N, Cusihuallpa MD, Montañez, Familiar C, Calle-Pascual AL. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. Diab Care 2014;37:2442–50.
42. Wu E-T, Nien F-J, Kuo C-H, Chen S-C, Chen K-Y, Chuang L-M, Li H-Y, Lee C-N. Diagnosis of more gestational diabetes lead to better pregnancy outcomes: comparing the International Association of the Diabetes and Pregnancy Study Group criteria, and the Carpenter and Coustan criteria. J Diab Inv. 2016;7:121–6.
43. Yumei W, Huixia Y, Weiwei Z, Hongyun Y, Haixia L, Jie Y, Cuilin Z. International Association of Diabetes and Pregnancy Study Group criteria is suitable for gestational diabetes mellitus diagnosis: further evidence from China. Chin Med J. 2014;127(20):3553–6.
44. Hoffman L, Nolan C, Wilson JD, Oats JJN, Simmons D. The Australasian diabetes in pregnancy society gestational diabetes mellitus management guidelines. Med J Aust. 1998;93–97:1998.
45. Nankervis A, McIntyre HD, Moses R, Ross GP, Callaway L, Porter C, Jeffries W, Boorman C, De Vries B, McElduff A for the Australasian Diabetes in Pregnancy Society. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia (as modified November 2014). http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf. Accessed 14 Feb 16.
46. Thompson D, Berger H, Feig D, Gagnon R, Kader T, Keely E, Kozak S, Ryan E, Sermer M and MD, Vinokuroff C. Diabetes and Pregnancy. Canadian Diabetes Association Clinical Practice Guidelines. Can J Diab. 2013;37(Suppl 1):S168–83.

Chapter 3
Evaluation of Glycemic Control Indexes During Pregnancy: The Role of HbA1c, Glycated Albumin, and Fructosamine

Maria Boyadzhieva

Key Points
The goal of the current chapter is to discuss:

- The role of HbA1c as index for glycemic control during pregnancy
- The role of fructosamine as index for glycemic control during pregnancy
- The role of glycated albumin as index for glycemic control during pregnancy

Keywords Gestational diabetes · Glycemic control · Glycated hemoglobin A1c · HbA1c · Glycated albumin · Fructosamine

Abbreviations

GDM	gestational diabetes mellitus
HbA1c	glycated hemoglobin A1c
GA	glycated albumin

Introduction

The incidence of diabetes worldwide has increased dramatically during the last years [1]. Estimates from the International Diabetes Federation indicate that the number of adults with diabetes in the world will expand by 55%, from 381.8 million in 2013 to 591.9 million in 2035. Therefore, there is also an increase in the prevalence of glucose intolerance during pregnancy. However, the occurrence of GDM parallels the prevalence of impaired glucose tolerance (IGT), obesity, and type 2 diabetes mellitus (T2DM) in a given population. With the implication of the International Association of the diabetes and pregnancy study groups (IADPSG) criteria, the prevalence of gestational diabetes (GDM) has increased to 17.8% [2]. These results are based on hyperglycemia and adverse pregnancy outcome (HAPO) study. In one study held in Bulgaria among high-risk pregnant women, the prevalence of GDM reached 29% [3]. The authors discuss the high prevalence results is due to selected high-risk population included in the study. The study was not epidemiological.

M. Boyadzhieva (✉)
Clinical Center of Endocrinology, USBALE "Acad. Ivan Penchev", Medical University of Sofia, 2 "Zdrave" str, 1431 Sofia, Bulgaria
e-mail: mariq_b@yahoo.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_3

Until recently, any degree of glucose intolerance or first recognition during pregnancy was defined as GDM [2]. In 2015, the International Federation of Gynecology and Obstetrics (FIGO) brought together experts to develop recommendations for diagnosis and treatment of glucose intolerance during pregnancy [4]. These recommendations must be adopted internationally. According to the new recommendations, hyperglycemia, which is first detected at any time during pregnancy should be classified either as diabetes mellitus in pregnancy or GDM. The disunion will lead to better care for those women who have pre-existing diabetes and related morbidities associated with diabetes in pregnancy.

The risks for the fetus during the intrauterine development are results of the level of maternal glycemia, which leads to fetal hyperglycemia. Thus stimulate the fetal pancreas to produce more insulin, and hence the rapid pace of growth and mismatch between the size of the fetus and gestational week (to the extent of macrosomia) with accumulation of fat, particularly abdominal located [5–7]. Uncontrolled maternal hyperglycemia and the developed hyperinsulinemia lead to hypoglecemia of the newborn [8]. Fetal macrosomia results in birth injuries, shoulder dystocia, as well as might be indication for caesarian delivery [9]. Glucose intolerance during pregnancy is also associated with increased risk of neonatal respiratory distress syndrome, microsomia or macrosomia, polycythemia, congenital malformations, hypocalcaemia, hypomagnesemia, severe jaundice [10]. Poor glycemic control is responsible for 49.2% of perinatal morbidity and mortality [11]. At a later stage of life, the offspring of women, who have had glucose intolerance during pregnancy, are at increased risk of obesity, impaired glucose tolerance—prediabetes, type 2 diabetes and cardiovascular disease [10, 12–15].

During pregnancy, women with glucose intolerance have higher risk for gestational hypertension, preeclampsia and eclampsia [10]. After completion of pregnancy, they have 40–60% higher risk for development of type 2 diabetes in the next 5–15 years, compared to a risk of 15% in the general population [16, 17].

Undoubtedly, hyperglycemia during pregnancy is a threat to the mother and fetus [2]. The individual approach is crucial for obtaining good glycemic control, thus how reducing the risk for the mother and her child. Currently, treatment of GDM or pre-existing diabetes is focused on healthy food intake, physical activity, and pharmacological treatment. In our clinical practice we test two types of indicators—blood glucose and glycated hemoglobin A1c (HbA1c), which covers blood excursions for longer period of time. Therefore, markers that more accurately reflect variations in blood glucose levels and mean glycemic status for short-term in GDM women are urgently required. Each indicator had its drawbacks. Blood sugar depends on many factors as nutrition, mental state, and stress. It varies significantly over time, which makes it suitable for the current moment and insufficient as a routine diagnostic indicator. The value of HbA1c during pregnancy is affected by erythrocytes shortened half-life and relative anemia as a result from hemodilution [18]. Usually, HbA1c provides information on the previous 2–3 months, which make it an indicator of low sensitivity during pregnancy. On the other hand, glycation of other proteins, such as albumin and fructosamin cover the glycemic control for the preceding 2–3 weeks. This makes it more feasible indicator of glycemic control in a dynamic condition, such as pregnancy. These indicators are not dependent from the half-life of erythrocytes. In HAPO study, there are no clear values with regard to evaluation of indicators of glycemic control. There is no adopted threshold of HbA1c, glycated albumin, or fructosamin for diagnosis of glucose intolerance during pregnancy.

Glycated Hemoglobin A1c (HbA1c)

Glycated hemoglobin is formed by non-enzymatic binding of glucose to the N-terminal valine of the β-chain of hemoglobin. Since the life span of a red blood cell is 120 days, HbA1c reflects a glucose concentration over the previous 2–3 months [19]. Fifty percent of HbA1c level is responsible for

glycemia during previous 1 month; 25% for the past 1–2 months and 25% for the last 2–4 months. Glycated hemoglobin A1c is an established clinical indicator representing the "gold standard" for assessing glycemic control in subjects with diabetes [20]. On international expert committee in 2008, consisting of representatives of the American Diabetes Association (ADA), International Diabetes Federation (IDF), and the European Association for the study of diabetes (EASD), experts have approved recommendations concerning the role of HbA1c in the diagnosis of diabetes. According to these recommendations, HbA1c $\geq$6.5% could be used for diabetes diagnosis. The HbA1c testing must be performed and certified by National Glycohemoglobin Standardization Program (NGSP). The test should be repeated except when there are symptoms of hyperglycemia or random blood glucose $\geq$11.1 mmol/l [21]. Based on this report, ADA in their annual standards of medical care for diabetes in 2010, introduce values of HbA1c $\geq$6.5% as diagnostic indicator for diabetes [22]. At the beginning of 2011, World Health Organization (WHO) published a report according to which HbA1c is introduced as diagnostic parameter for diabetes with threshold value of 6.5%. It is also clarified that under this value diabetes is not excluded, when we have diabetes, diagnosed on the basis of plasma glucose and/or OGTT using WHO criteria [23]. More often, HbA1c is used in patients with prediabetes (HbA1c 5.7–6.4%) [24]. For the Bulgarian population, Tankova et al. [25] have set threshold of $\geq$5.5% (sensitivity 71% and specificity 64%) for the diagnosis of prediabetes and 6.1% (sensitivity 86% and specificity 92%) for diabetes diagnosis. Similar results have been found from other study groups.

Since pregnant women most often are not included in surveys, less data is available regarding the importance of HbA1c in clinical practice. Results from studies and meta-analysis revealed a significant and independent relationship between HbA1c levels and incidence of GDM, which is in ranges lower than those found for diabetes diagnosis [26, 27]. According to our data, we found significantly higher levels of HbA1c in GDM group, compared to controls of pregnant women. These values are significantly lower than those described in the literature for patients with newly diagnosed diabetes. Therefore, it is necessary that a separate threshold value of HbA1c is set for GDM diagnosis and its implication as a screening indicator for disorders in glucose tolerance during pregnancy. Optimal sensitivity (64.7%) and specificity (62%) for the diagnosis of GDM was found at the threshold of HbA1c $\geq$5.6% (Table 3.1; Fig. 3.1). However, about 1/3 of the subjects had a false negative and in another 1/3 false positive results. Similarly, Rajput et al. [28] have found threshold of 5.95% for diagnosis of GDM and optimal sensitivity and specificity with HbA1c 5.45%. In a recent study, which have enrolled 1959 pregnant women with prevalence of GDM 21%, have found 95% specificity for HbA1c using value of $\geq$5.5%, but very low sensitivity 14.8% [29]. Adequate sensitivity

Table 3.1 Distribution of pregnant women according to different values of HbA1c

HbA1c on or under the threshold (%)	4.6%	5%	5.3%	5.6%	6%	6.5%
Number of women on or under the threshold	291 (100%)	278 (95.7)	249 (85.6)	188 (64.7)	106 (36.4)	33 (11.2)
False negative results	0	4.3	14.4	35.3	63.6	88.8
Sensitivity	100	95.72	85.56	64.71	36.36	11.23
Positive predictive value	47.46	48.25	53.16	60.5	82.93	91.3
Number of women under the treshold	0 (0%)	8	27	66	119	166
False positive results	100	92.3	67.8	38.0	6.7	1
Specificity	0.48%	7.69%	32.21	62.02	93.27	99.04
Negative predictive value	100	66.67	71.28	66.15	61.98	55.38

Selected values of HbA1c and relevant tests for sensitivity, specificity, positive and negative predictive value, false positive result (1—specificity) and false negative results (1—sensitivity)

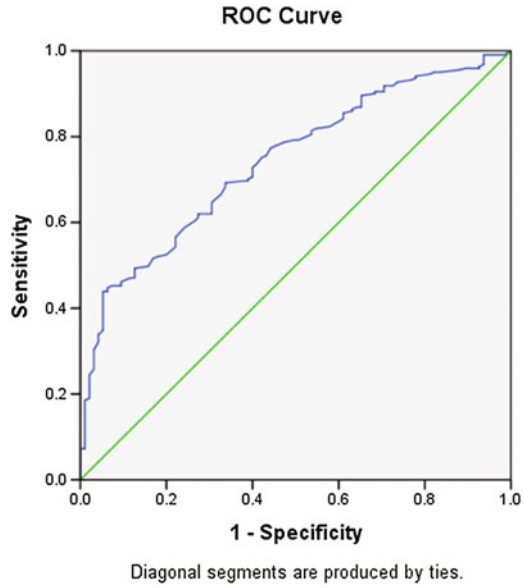


Fig. 3.1 ROC for HbA1c. Receiver operating characteristic curve demonstrating the plot between sensitivity and specificity for HbA1c levels during pregnancy as a predictor for glucose intolerance during pregnancy

(85%) to exclude GDM was cut-off value <4.8%, but again with low specificity (31.8%). Aldasouqi et al. [30] found that in those women who remain undiagnosed by HbA1c value, the risk for developing adverse pregnancy outcomes is minimal. Therefore, women with HbA1c values between 5 and 6% should undergo diagnostic OGTT. Furthermore, those women with an abnormal HbA1c will require a confirmatory OGTT. According to Mathiesen et al. [31], women with HbA1c > 5.6% have threefold higher risk of fetal macrosomia and sixfold higher risk for fetal hypoglycemia, compared to pregnant women with lesser than 5.6% HbA1c.

We found significant positive correlation between HbA1c and fasting plasma glucose, and 120 min during the OGTT. Ye et al. [29] found that HbA1c level was significantly associated with the risk of preterm delivery, neonatal hyperbilirubinemia, and neonatal asphyxia. These data indicate that HbA1c and OGTT are complementary. Similar results are established in a number of studies which main purpose is to define the threshold of HbA1c for prediabetes (impaired fasting glucose and/or impaired glucose tolerance) [32]. These data give us reason to assume that GDM could be considered as prediabetes similar to impaired fasting glucose or impaired glucose tolerance.

O'Shea et al. [33] determine trimester specific levels of HbA1c based on the study of 311 subjects, of whom 246 pregnant women and 65 non-pregnant controls. They divided pregnant women into three groups based on gestational age—I, II and III trimester. The authors defined reference intervals of HbA1c for healthy controls—4.8–5.5%, for I trimester—4.3–5.4%, for II trimester—4.4–5.4% and for the III trimester 4.7–5.7%. The HbA1c reference intervals were significantly lower in pregnant women compared to control group. Conducting retrospective analysis, the same authors found that in 46% of pregnant women who have had GDM (IADPSG criteria), measurement of HbA1c alone was enough for GDM diagnosing. Therefore, the authors recommend the routine administration of examination of HbA1c in II trimester of pregnancy as a diagnostic marker for GDM. With its introduction into clinical practice the number of ongoing OGTT might decrease [33].

The New Zealand healthcare system has introduced HbA1c as a screening tool for pre-existing diabetes. According to their guideline, all pregnant women should be tested for undiagnosed diabetes using HbA1c prior to 20 weeks of gestation. Those who have HbA1c $\geq$6.7% should be considered as diabetes and must be referred to pregnancy diabetes clinic [34].

Glycated hemoglobin A1c has not yet been adopted as an indicator for diagnosis of glucose intolerance during pregnancy. It is known that its level might be reduced as a result of fetal–placental glucose utilization, shortened life of erythrocytes and pregnancies with diabetes—improved glycemic control [35, 36]. However, some studies in pregnant women with and without pre-existing diabetes have observed a rise in the level of HbA1c from the beginning of second and third trimester [36, 37]. One of the main disadvantages of HbA1c is the biphasic changes in its level during pregnancy and the lowest level set at 24 weeks of gestation [38]. On the other hand, HbA1c is also increased in the presence of iron deficiency anemia, which often occurs during pregnancy, irrespective of the level of blood glucose [37].

In women who have GDM and those who have an increased risk for developing such, HbA1c can be an indicator of poor outcome of pregnancy and/or postpartum development of diabetes. Despite the accumulated evidence up to date, there are no established recommendations for the use of HbA1c in the diagnostic approach of glucose intolerance during pregnancy.

Glycated Albumin (Ga)

Glycated albumin is ketamin, which is formed in the non-enzyme glycosilation between four lysine span of albumin with glucose. It is formed in a similar mechanism as HbA1c, but the affinity for binding the albumin with glucose is 4.5 times higher than that of hemoglobin with glucose [39]. Because the half-life of GA is about 12–19 days, it will be an indicator of glycemic control for the previous 2–3 weeks versus 2–3 months for HbA1c. A study by Pan et al. [40], in which 713 pregnant women have been enrolled, showed that compared with HbA1c, GA is more closely correlated with fasting and postprandial glucose, regardless of insulin resistance and might be a better monitoring index in women with GDM. These results have been confirmed also by Hashimoto et al. [37], especially as a better indicator of postprandial blood glucose compared to HbA1c.

Pregnancy is a dynamic state that requires constant monitoring and therefore GA will better reflect the level of glycemia. In the normal course of pregnancy, iron deficiency progresses gradually, leading to false higher levels of HbA1c. This makes HbA1c unreliable indicator, especially in the final stages of pregnancy. When there is an exogenous iron supplementation, such changes in the level of HbA1c might not be observed. On the other hand, Hashimoto et al. [41] found that GA is not dependent from iron deficiency and the anemia trough the pregnancy. However, we must not ignore the fact that GA is influenced by the metabolism of albumin. Particular attention should be considered regarding cases with nephrotic syndrome, as well as abnormalities in thyroid function. It is known that compared with HbA1c, glycated albumin (GA) is superior in estimating glycemic control in diabetic patients on hemodialysis.

In another study of Hashimoto et al. [39], the authors aimed to analyze the relationship between indicators of glycemic control and pregnancy outcome. They found a linear relationship between GA and unfavorable outcome of pregnancy. The authors take the upper threshold of both indicators of glycemic control in the normal course of pregnancy (HbA1c 5.7% and GA 15.7%) and in terms of neonatal complications—the frequency of neonatal hypoglycemia, polycythemia, and respiratory distress syndrome. They observed a higher incidence of complications if the value of GA exceeded 15.7% versus lower incidence if the GA is lower than 15.7%. Such linear relationship is not apparent among women with HbA1c > 5.7% versus < 5.7%. In another study of Hua-Ping et al. [42], in which 2118 pregnant women have been enrolled, using a cut-off 11.6% for GA (area under the receiver operating characteristic curve was 0.874; 95% confidence interval 0.811–0.938), the sensitivity and specificity for detecting a poor glycemic control were 75.93 and 86.36%, respectively. The risk of birth weight $\geq$3500 g and macrosomia increased significantly with GA levels $\geq$13.00% at 24–28 weeks and $\geq$12.00% at 36–38 weeks of gestation. Both study groups believe that additional analysis and assessment of iron status, but GA has proved as more reliable indicator regarding the adverse outcome of pregnancy [39].

In patients with type 1 or type 2 Yoshiuchii et al. [43] confirm the relationship between GA and blood sugar and between HbA1c and blood sugar; GA was a better indicator for monitoring of blood glucose in patients with diabetes. In the diagnosis of diabetes, some authors suggest that serum GA measurements can be used to determine the need of an OGTT. Enrolling 1559 subjects not known to have diabetes or to use anti-diabetic medications, Wu et al. [44] measured GA and performed OGTT. They set threshold of serum GA 15% with sensitivity 74%, specificity 85%, and area under the receiver operating characteristic 0.86 for diabetes diagnosis.

In certain patients there is a glycemic gap and parallel measurement of GA and HbA1c would give a more accurate assessment of the level of glycemia. The glycation gap is an empirical measure of the extent of the difference between HbA1c and fructosamine levels. Several studies have shown that the presence of the gap is linked to diabetic nephropathy, but possible artifacts caused by dependence of the fructosamine level on the extent of serum protein metabolism require careful consideration. Kim et al. [45] investigated the consistency of glycation gaps measured by assaying GA levels and based on several measurements of both HbA1c and GA on 171 Koreans. They came to conclusion that the gap is consistent within an individual over time. The glycation gap was associated with visceral fat and kidney function in patients with type 2 diabetes.

The regular monitoring of GA in women with glucose intolerance during pregnancy (once every 3–4 weeks) will help to reduce the frequency of self-monitoring of blood glucose and thus how to lower healthcare costs, and increase patient compliance. Glycated hemoglobin A1c is not an accurate indicator of glycemic control in all patients with diabetes.

Fructosamine

For the first time, Peterson in 1977 describes glycation of proteins, which have shorter half-life compared to hemoglobin and which could be a marker for glycemic control during pregnancy [46]. He found that albumin is a protein which undergoes the greatest extent of glycation. Using the term fructosamine should be perceived glycoalbumin and the total glycosylated protein. The main component of fructosamine is glycated albumin, but fructosamine contains other components such as glycated lipoprotein and glycation globulin. Fructosamine is not influenced by anemia or abnormal hemoglobin. Fructosamine measurement is quick, technically simple, inexpensive, precise, fairly free of interferences, unaffected by red blood diseases and easily automated for use with microsample volumes.

Both fructosamin and HbA1c are used for evaluation of glycemic control, but since the half-life of glycated hemoglobin is 6–8 weeks, it reflects glycemic control over a longer period of time versus frucotsamine, whose half-life is only 2–3 weeks. Because of the short half-life of fructosamine, it has a greater sensitivity to the rapidly occurring changes during pregnancy. Hughes et al. [47] achieved a 79.4% sensitivity and a 77.3% specificity of fructosamine for a diagnosis of GDM confirmed by a glucose tolerance test using Carpenter's modified criteria. In view of the organizational simplicity of this test requirement, a wider evaluation is suggested together with a re-evaluation of clinical outcome criteria rather than blood glucose levels alone.

Agarwal et al. conducted study on 430 pregnant women and found that lower cut-off values for fructosamine of 210 micromol/l and HbA1c 5%, the sensitivities achieved were 92.2 and 92.1% while the negative predictive values were 88.9 and 86.9%, respectively. The upper cut-off values did not achieve acceptable positive predictive values to be useful for ruling in GDM. They concluded that this screening approach would be clinically useful and more acceptable to patients in selected high-risk populations. The same group conducted another study in 2011 with 849 pregnant women enrolled and they found high sensitivity, but low specificity, which required carrying out the OGTT in every

4 out of 5 women who are at risk for development GDM [48]. Despite its high sensitivity, however, the fructosamine has not proven its specificity as a diagnostic indicator for glucose intolerance during pregnancy.

Conclusion

We believe that the use of HbA1c alone cannot be recommended for the diagnosis of glucose intolerance during pregnancy. When HbA1c is in range 5-6% we should undergo OGTT. There are several factors that make HbA1c unreliable marker for screening during pregnancy, some of which are shortened half-life of red blood cells, relative anemia due to hemodilution, gestational week, and the existence of an iron deficiency. The study of GA as an indicator for assessing glucose control can contribute both to the diagnosis of GDM and for monitoring glycemic control in pregnant women with GDM and diabetes. The short half-life of GA gives priority over HbA1c in a dynamic condition, such as pregnancy. It is necessary to conduct an epidemiological study, which apart from setting referral ranges will prove the role of GA during pregnancy.

Recommendations and Guidelines

- In patients with diabetes glycated hemoglobin A1c (HbA1c) is a "gold standard" for diagnosis and evaluation of glycemia for past period of time.
- HbA1c values during pregnancy are significantly lower than those described in the literature for patients with newly diagnosed diabetes.
- HbA1c alone cannot be recommended for the diagnosis of glucose intolerance during pregnancy.
- Some authors suggest trimester specific levels of HbA1c and recommend the routine administration of HbA1c measurement in second trimester of pregnancy as a diagnostic marker for GDM, thus how decreasing number of ongoing OGTT.
- The disadvantages of HbA1c as a reliable parameter during pregnancy are related to increased iron deficiency, biphasic changes in its level during pregnancy and unreached maximal sensitivity and specificity;
- Perform OGTT when HbA1c is in range 5–6%.
- Glycated albumin might be a better indicator for glycemic control during dynamic changes in pregnancy due to shortened half-life of albumin and higher binding affinity with glucose compared to HbA1c.
- Studies show that glycated albumin might be a better indicator of postprandial blood glucose compared to HbA1c.
- In certain patients there is a glycemic gap and parallel measurement of GA and HbA1c would give a more accurate assessment of the level of glycemia.
- The clinical significance of glycated albumin should be studied carefully for future implementation in diagnostic criteria of glucose intolerance during pregnancy.
- Fructosamine have shorter half-life compared to HbA1c and is not influenced by anemia or abnormal hemoglobin.
- Fructosamine has high sensitivity, but low specificity, which requires additional OGTT in women with risk for GDM development.
- HbA1c reflects glycemic control over a longer period of time compared to fructosamine and GA, but this might be unfavorable in dynamic conditions such as pregnancy.

Acknowledgements The author's work presented here has been funded under grant: DO 02/7 2008 National Science Fund, Ministry of Education and Science.

References

1. International Diabetes Federation. IDF Diabetes Atlas 6th ed., URL: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf, 2013.
2. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiler JL, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676–82.
3. Boyadzhieva MV, Atanasova I, Zacharieva S, Tankova T, Dimitrova V. Comparative analysis of current diagnostic criteria for gestational diabetes mellitus. Obstet Med. 2012;5(2):71–7.
4. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, Cabero Roura L, McIntyre HD, Morris JL, Divakar, H. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet (2015);131(3):30007–2.
5. Jarrett RJ. Reflections on gestational diabetes mellitus. Lancet. 1981;2(8257):1220–1.
6. Hunter DJ. Screening for gestational diabetes. Am J Obstet Gynecol. 1989;161(5):1423–4.
7. Spellacy WN, Miller S, Winegar A, Peterson PQ. Macrosomia–maternal characteristics and infant complications. Obstet Gynecol. 1985;66(2):158–61.
8. Cordero L, Landon MB. Infant of the diabetic mother. Clin Perinatol. 1993;20(3):635–48.
9. Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J. Gestational diabetes mellitus. A survey of perinatal complications in the 1980s. Diabetes. 1991;2:74–8.
10. Davey RX, Hamblin PS. Selective versus universal screening for gestational diabetes mellitus: an evaluation of predictive risk factors. Med J Aust. 2001;174(3):118–21.
11. Ferrara A, Hedderson MM, Quesenberry CP, Selby JV. Prevalence of gestational diabetes mellitus detected by the national diabetes data group or the carpenter and coustan plasma glucose thresholds. Diabetes Care. 2002;25 (9):1625–30.
12. Opara PI, Jaja T, Onubogu UC. Morbidity and mortality amongst infants of diabetic mothers admitted into a special care baby unit in Port Harcourt, Nigeria. Ital J Pediatr. 2010;36(1):77.
13. Vohr BR, McGarvey ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4–7 years of age. Diabetes Care. 1999;22(8):1284–91.
14. Schaefer-Graf UM, Pawliczak J, Passow D, Hartmann R, Rossi R, Buhrer C, Harder T, Plagemann A, Vetter K, Kordonouri O. Birth weight and parental BMI predict overweight in children from mothers with gestational diabetes. Diabetes Care. 2005;28(7):1745–50.
15. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3):e290–6.
16. Metzger, B.E., T.A. Buchanan, D.R. Coustan, A. de Leiva, D.B. Dunger, D.R. Hadden, M. Hod, J.L. Kitzmiller, S. L. Kjos, J.N. Oats, et al., Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care, 2007;30 Suppl(2): S251–60.
17. O'Sullivan JB. Diabetes mellitus after GDM. Diabetes. 1991;40(Suppl 2):131–5.
18. Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. Blood. 1982;59(6):1348–50.
19. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care. 2011;34(2):518–23.
20. Hanas R, John G. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care. 2010;33(8):1903–4.
21. Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes: Diabetes Care 2009;32(7):1327–1334. Clin Biochem Rev, 2009;30(4):197–200.
22. Standards of medical care in diabetes–2010. Diabetes Care, 2010;33 Suppl 1:S11–61.
23. Organosation WH, Use of Glycated hemoglobin (HbA1c) in the diagnosis of diabetes mellitus. 2011.
24. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet. 2011;378(9786):169–81.
25. Ц АТ, *Оценка на общ и индувидуален риск за захарен диабет.* Дисертационен труд за присъждане на научна степен. Доктор на медицинските науки 2012.
26. Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes: a reappraisal of HBA1c as a screening test. Acta Obstet Gynecol Scand. 2005;84(12):1159–63.
27. Moses RG. HbA1c and the diagnosis of gestational diabetes mellitus–a test whose time has not yet come. Diabetes Res Clin Pract. 2012;98(1):3–4.

28. Rajput R, Yogesh Y, Rajput M, Nanda S. Utility of HbA1c for diagnosis of gestational diabetes mellitus. Diabetes Res Clin Pract. 2012;98(1):104–7.
29. Ye M, Liu Y, Cao X, Yao F, Liu B, Li Y, Wang Z, Xiao H. The utility of HbA1c for screening gestational diabetes mellitus and its relationship with adverse pregnancy outcomes. Diabetes Res Clin Pract. 2016;114:43–9.
30. Aldasouqi SA, Solomon DJ, Bokhari SA, Khan PM, Muneera S, Gossain VV. Glycohemoglobin A1c: A promising screening tool in gestational diabetes mellitus. Int J Diabetes Dev Ctries. 2008;28(4):121–4.
31. Mikkelsen MR, Nielsen SB, Stage E, Mathiesen ER, Damm P. High maternal HbA1c is associated with overweight in neonates. Dan Med Bull, 2011;58(9).
32. Sarwar N, Aspelund T, Eiriksdottir G, Gobin R, Seshasai SR, Forouhi NG, Sigurdsson G, Danesh J, Gudnason V. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik prospective study and systematic review. PLoS Med. 2010;7(5):1000278.
33. O'Shea P, O'Connor C, Owens L, Carmody L, Avalos G, Nestor L, Lydon K, Dunne FP. Trimester-specific reference intervals for IFCC standardised haemoglobin A(1c): new criterion to diagnose gestational diabetes mellitus (GDM)? Ir Med J. 2012;105(5 Suppl):29–31.
34. Rowan J, Allen H, Budden A, Elder R, Farrant M, Hughes R, Ivanova V, Moore P, Marnoch C, McGrath N. New Zealand National GDM Guidelines: an alternative view of some good practice points. Aust N Z J Obstet Gynaecol. 2015;55(1):17–20.
35. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, Lee YJ, Holmes L, Simpson JL, Metzger B. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. Metabolism. 1998;47(9):1140–4.
36. Lurie S, Mamet Y. Red blood cell survival and kinetics during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2000;93(2):185–92.
37. Hashimoto K, Noguchi S, Morimoto Y, Hamada S, Wasada K, Imai S, Murata Y, Kasayama S, Koga M. A1C but not serum glycated albumin is elevated in late pregnancy owing to iron deficiency. Diabetes Care. 2008;31 (10):1945–8.
38. Phelps RL, Honig GR, Green D, Metzger BE, Frederiksen MC, Freinkel N. Biphasic changes in hemoglobin A1c concentrations during normal human pregnancy. Am J Obstet Gynecol. 1983;147(6):651–3.
39. Hashimoto K, Koga M. Indicators of glycemic control in patients with gestational diabetes mellitus and pregnant women with diabetes mellitus. World J Diabetes. 2015;6(8):1045–56.
40. Pan J, Zhang F, Zhang L, Bao Y, Tao M, Jia W. Influence of insulin sensitivity and secretion on glycated albumin and hemoglobin A1c in pregnant women with gestational diabetes mellitus. Int J Gynaecol Obstet. 2013;121 (3):252–6.
41. Hashimoto K, Osugi T, Noguchi S, Morimoto Y, Wasada K, Imai S, Waguri M, Toyoda R, Fujita T, Kasayama S, et al. A1C but not serum glycated albumin is elevated because of iron deficiency in late pregnancy in diabetic women. Diabetes Care. 2010;33(3):509–11.
42. Li HP, Wang FH, Tao MF, Huang YJ, Jia WP. Association between glycemic control and birthweight with glycated albumin in Chinese women with gestational diabetes mellitus. J Diabetes Investig. 2016;7(1):48–55.
43. Yoshiuchi K, MM, Katakami N, Nakatani Y, Sakamoto K, Matsuoka T, Umayahara Y, Kosugi K, Kaneto H, Yamasaki Y, et al. Glycated albumin is a better indicator for glucose excursion than glycated hemoglobin in type 1 and type 2 diabetes. Endocr J. 2008;55: 503–507.
44. Wu WC, Ma WY, Wei JN, Yu TY, Lin MS, Shih SR, Hua CH, Liao YJ, Chuang LM, Li, HY. Serum Glycated Albumin to Guide the Diagnosis of Diabetes Mellitus. PLoS One. 2016;11(1).
45. Kim MK, Yun KJ, Kwon HS, Baek KH, Song KH. Discordance in the levels of hemoglobin A1C and glycated albumin: Calculation of the glycation gap based on glycated albumin level. J Diabetes Complications. 2016;30 (3):477–81.
46. Peterson CM, Jones RL. Minor hemoglobins, diabetic "control", and diseases of postsynthetic protein modification. Ann Intern Med. 1977;87(4):489–91.
47. Hughes PF, Agarwal M, Newman P, Morrison J. An evaluation of fructosamine estimation in screening for gestational diabetes mellitus. Diabet Med. 1995;12(8):708–12.
48. Agarwal MM, Dhatt GS, Othman Y, Ljubisavljevic MR. Gestational diabetes: an evaluation of serum fructosamine as a screening test in a high-risk population. Gynecol Obstet Invest. 2011;71(3):207–12.

Chapter 4
Mental Health and Diabetes During Pregnancy: Is It Chicken or Egg?

Hannah Grace Dahlen and Charlene Thornton

Key Points

- There is a bidirectional relationship between diabetes and depression in non-pregnant adults and in women in particular.
- There has been little investigation into whether this bidirectional relationship also exists for pregnant women who develop gestational diabetes during the pregnancy.
- Gestational diabetes is increasing and can add significant morbidity for childbearing women and/or their babies.
- A recent association has been found between having an Edinburgh Perinatal Depression Scale (EPDS) $\geq$13 at booking in for pregnancy care and the diagnosis of gestational diabetes at around 28 weeks of pregnancy.
- The underlying mechanism for this link needs to be established and confirmed in longitudinal studies
- Models of care that promote body/mind dualism need to be challenged.

Keywords Diabetes · Gestational diabetes · Depression · Mental health · Pregnancy

Abbreviations

GDM Gestational diabetes mellitus
EPDS Edinburgh perinatal depression scale
BMI Body mass index

Introduction

Diabetes and Depression

The bidirectional relationship between diabetes and depression has been shown in several studies of both non-pregnant and pregnant adults. Systematic reviews indicate a doubling in the likelihood of

H.G. Dahlen · C. Thornton
School of Nursing and Midwifery, Western Sydney University,
Locked Bag 1797, Penrith, NSW 2751, Australia
e-mail: c.thornton@westernsydney.edu.au

H.G. Dahlen (✉)
Ingham Institute, Liverpool, NSW, Australia
e-mail: h.dahlen@westernsydney.edu.au

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_4

depression in people with diabetes. Anderson et al. (2001) undertook a meta-analysis of 20 controlled, cross-sectional studies with non-diabetic comparison groups and found the likelihood of depression in the diabetic group was twice that of the non-diabetic group (OR 2.0 [95% CI 1.8–2.2]) [1]. This did not vary by assessment method, gender or subject source and interestingly the rates of depression were very similar between type 1 and type 2 diabetics despite obvious differences in ages, management and co-morbidities. Ali et al. (2006) undertook a systematic review and meta-analysis of community based, large scale, prospective studies and similarly found significantly increased rates of depression in people with type 2 diabetes when compared to control subjects (17.6% vs. 9.8%, OR = 1.6 [95% CI 1.2–1.00]) [2]. However, only one study included in this review reported adjusted prevalence rates for potential confounders such as age, gender, co-morbid disease and weight. Rustad et al. (2011) undertook a systematic review of the relationship between depression and diabetes and the neurochemical underpinnings of the two disorders, concluding that depression and diabetes should be treated together rather than as isolated diseases. They conclude the mind/body dualism is a false economy and a team-based approach is needed to address both issues [3]. Rustad et al. (2011) call for more longitudinal, prospective studies to determine causal factors. Rustad et al. (2011) points out that many of the large-scale studies use dimensional rating scales to measure depressive symptoms rather than structured diagnostic psychiatric interviews.

Research into older adults indicated this relationship between diabetes and depression and depression and diabetes is conflicting. Campayo et al. (2010) followed a community of adults over 55 years of age in Spain and used a psychiatric interview and the Geriatric Mental State Schedule, controlling for potential confounders and found an increased incidence of diabetes amongst participants with depression (non-severe depression, persistent depression and untreated depression) [4]. Golden et al. (2008) found the risk of type 2 diabetes was 1.10 times higher for each 5 unit increment in the Centre for Epidemiological Studies Depression (CES-D) Scale [5]. However, this association was no longer significant following adjustment for lifestyle factors. These studies seem to support the bidirectional relationship between type 2 diabetes and depression. This has been described as depression acting as an independent risk factor for the development of type 2 diabetes and type 2 diabetes and its associated health challenges being associated with depression [6]. Rhee et al. (2008) found no association between depressive symptoms using the PHQ and previously undiagnosed glucose intolerance in over 1000 subjects in a cross-sectional study. A meta-analysis exploring the bidirectional hypothesis by Mezuk et al. (2008) found an increased risk of developing type 2 diabetes in patients who had depressive symptoms. In 13 of the papers included that met eligibility for baseline depression predicting the onset of diabetes, the relative risk was (RR 1.60 [95% CI 1.37–1.88]). For seven papers that showed type 2 diabetes occurring before the onset of depression, the risk of depression only increased modestly (RR 1.15 [95% CI 1.02–1.30]) [7]. However, once again the relevance of these findings to pregnant women and gestational diabetes is unknown.

Gender, Diabetes and Depression

Studies examining diabetes in women specifically have also found a bidirectional diabetes–depression relationship. In a study of 55,000 US women aged 50–75 years of age over 10 years, and adjusting for confounders, researchers found depression and diabetes were closely related to each other and this reciprocal association depended on the severity or treatment of each condition [8]. In this study the researchers found depression had an effect on the incidence of diabetes, independent of adiposity and physical activity levels. Those treated with antidepressant medication were at even higher risk of developing type 2 diabetes. Whether this is due to the fact that antidepressant use reflects the severity of the depression or antidepressants exert some clinical effects on glucose homeostasis is still debated.

Pregnancy, Diabetes and Depression

Most of these studies and reviews to date that look at diabetes and depression do not address gestational diabetes (GDM), which is unique to women who are pregnant and generally resolves following the birth. A link between a previous history of depression and GDM has been found recently in a large multiethnic US retrospective cohort study [9]. Bowers et al. (2013) found in a population of 121,260 women that a history of depression was significantly associated with an increased risk of developing GDM (AOR 1.42; 95% CI 1.26–1.60). When adjusted for pre-pregnancy BMI and weight gain during the pregnancy the association weakened, though it remained significant [9]. There is also some evidence that treating GDM reduces the risk for postpartum depression [10].

Perinatal Mental Health

In Australia one in five women with a full-term infant has a current mental health condition or meets the DSM-V criteria for perinatal mental health problems in the first year following birth [11, 12]. Similar statistics are reported for other countries [13]. Two-thirds of women with depression or anxiety following the birth have been found to be symptomatic during the pregnancy, with migrant women more likely to be affected with postnatal depression (PND) (24–42% compared to 10–15%) [12, 14, 15].

In NSW Australia, in response to recognition of the importance of social and emotional problems in the perinatal period several states have introduced a routine psychosocial assessment, including depression screening [17]. In NSW, the *Supporting Families Early Policy* integrates psychosocial risk assessment with routine care (Integrated Perinatal Care (IPC)) during pregnancy and following birth. A coordinated network of support and services for mothers and their babies has been put in place [16, 17]. All women receive this assessment from midwives at the antenatal booking visit, then from the Child and Family Health Nurse at a routine home visit following birth. Six to eight weeks following the birth another check is undertaken in the Early Childhood Centre. This psychosocial screen includes the Edinburgh Perinatal Depression Scale (EPDS) and questions that reflect seven key variables or domains of risk (Table 4.1).

The EPDS is a 10-item self-report scale that is widely used in maternity services [18]. The EPDS was devised for screening women for depression in the postnatal period but has subsequently been validated for use in the antenatal period. The women complete the simple 10-point questionnaire themselves and the practitioner then allocates a score. The maximum score is 30 and those who score greater than 12 are generally considered to meet the criteria for depression [18]. Due to its simplicity and versatility it has become one of the most common screening tools for depression birth during pregnancy and during the postpartum period. There has also been validation with several cultural groups. Migrants, refugees and asylum seekers appear to have higher EPDS [14].

So What About GDM and Mental Health During Pregnancy?

GDM

Gestational diabetes (GDM) is an impaired carbohydrate metabolism that occurs during pregnancy. GDM is generally screened for in Australia between 26 and 28 weeks of pregnancy. GDM is a common pregnancy complication that affects between 7–14% of pregnant women. The prevalence of GDM has increased significantly in the Australian population from 4.6% in 2005, to 5.6% in 2010

Table 4.1 Psychosocial risk variables I–VII. NSW Department of Health (2009)

Variables (Risk factors)	Suggested format for psychosocial assessment questions
I. Lack of support	1. Will you be able to get practical support with your baby?
	2, Do you have someone you are able to talk to about your feelings or worries?
II. Recent major stressors in the last 12 months	3. Have you had any major stressors, changes or losses recently (i.e. in the last 12 months) such as, financial problems, someone close to you dying, or any other serious worries?
III. Low self-esteem (including lack of self-confidence, high anxiety and perfectionistic traits)	4. Generally, do you consider yourself a confident person?
	5. Does it worry you a lot if things get messy or out of place?
IV. History of anxiety, depression or other mental health problems	6a. Have you ever felt anxious, miserable, worried or depressed for more than a couple of weeks?
	6b. If so, did it seriously interfere with your work and your relationships with friends and family?
	7. Are you currently receiving, or have you in the past received, treatment for any emotional problems?
V. Couple's relationship problems or dysfunction (if applicable)	8. How would you describe your relationship with your partner?
	9a. Antenatal: What do you think your relationship will be like after the birth OR
	9b. Postnatal (in community health setting): Has your relationship changed since having the baby?
VI. Adverse childhood experiences	10. Now that you are having a child of your own, you may think more about your own childhood and what it was like
	As a child were you hurt or abused in any way (physically, emotionally, sexually)?
VII. Domestic violence	11. Within the last year have you been hit, slapped, or hurt in other ways by your partner or ex-partner?
Questions must be asked only when the woman can be interviewed away from partner or family member over the age of 3 years. Staff must undergo training in screening for domestic violence before administering questions	12. Are you frightened of your partner or ex-partner? (If the response to questions 11 and 12 is "No" then offer the DV information card and omit questions 13–18)
	13. Are you safe here at home?/to go home when you leave here?
	14. Has your child/children been hurt or witnessed violence?
	15. Who is/are your children with now?
	16. Are they safe?
	17. Are you worried about your child/children's safety?
	18. Would you like assistance with this?
Opportunity to disclose further	19. Are there any other issues or worries you would like to mention?

and 7.5% in 2015 [19, 20]. This increasing incidence is also evident in most developed countries. In the United States the incidence was 9.2% in 2014 [21]. The changing socio-economic profile of the developing world has also led to increases in countries such as China, where rates are now 9.3%, which is a 3.5 fold increase since 1999 [22]. Women from Southeast Asia seem to have a consistently

higher rate of GDM than other groups. Carolan (2013) found in a systematic review that the rate of GDM was consistently higher among Southeast (SE) Asian born women than women from the same ethnic background born in developed nations, such as the United States of America (USA), the United Kingdom (UK) and Australia [23].

GDM is associated with complications such as increased birth weight, macrosomia, caesarean birth and preterm birth [24, 25]. Women who are diagnosed with GDM have a 48% development rate to type 2 diabetes within the 10-year period following pregnancy [26], with lifestyle intervention ± treatment with metformin only reducing this risk to 40%. GDM during pregnancy increases the risk of other complications such as pre-eclampsia with an OR for preeclampsia in women with GDM of 1.5 (95% CI 1.1–2.1). There is also a positive correlation between the risk of developing pre-eclampsia with increasing maternal BMI in women with GDM [27]. Increasingly health workers in maternity services are reporting the expansion of clinics for pregnant women with GDM and impact on women and babies in terms of medical interventions during pregnancy, birth and the postpartum period.

Perinatal Mental Health and GDM

There are very few studies examining the link between depression and GDM [9, 28, 29]. There is some evidence that treating GDM reduces the risk for postpartum depression [10] and that having a pre-existing history of depression increases the risk of GDM during pregnancy [9].

The study we undertook and published recently [30] used data from one Sydney hospital (2012–2013) of all births recorded in the ObstetriX™ database (routinely collected data) (n = 3092). Demographics, obstetric and psychosocial risk profile, obstetric interventions and complications and selected maternal and neonatal outcomes were examined for women born in Australia and overseas. We found an association between having an Edinburgh Postnatal Depression Scale (EPDS) ≥ 13 when booking in for pregnancy care between 12 and 17 weeks of pregnancy and other psychosocial issues, such as thoughts of self-harm, domestic violence, childhood abuse, etc. These women were also less likely to breastfeed. Women with an EPDS ≥ 13 at booking compared to women with EPDS ≤ 12 had a higher chance of being diagnosed with GDM when controlled for smoking, parity, maternal age, BMI and ethnicity (AOR 1.85 95% CI 1.14–3.0). We could not control for psychiatric medications that may have indicate severity and/or contributed to an increased risk of developing GDM. This is the first study we know of showing an association between having an Edinburgh Perinatal Depression Scale (EPDS) ≥ 13 at booking in for pregnancy care (12–17 weeks) and the diagnosis of GDM at around 28 weeks of pregnancy [30], when adjusted for parity, smoking, maternal weight, age and ethnicity. Table 4.2 is reproduced from our published paper [30].

All significant ORs adjusted for smoking (yes/no), primip (yes/no), age (<20, 20–34, ≥ 35), BMI (obese yes/no), born in Australia (yes/no).

What Is the Pathophysiology?

The underlying mechanism for this link needs to be established [8]. A similar bidirectional association has been found between depression and Metabolic Syndrome (central obesity, hyperglycemaia, elevated blood pressure, hypertriglyceridemia, decreased HDL Cholesterol) [31] and depression and insulin resistance [32]. The pathophysiology of this link could be due to hypothalamic pituitary adrenal axis hyperactivity (HPA) and mental stress induced sympathomedullary activation in patients with major depression leading to decreased glucose transport and insulin resistance. Cortisol and catecholamines are also increased with mental stress, and depression causes inactivity, which combine with increased cortisol levels, increased adiposity and insulin resistance [3]. Some psychiatric

Table 4.2 Odds ratio calculations for women with an EPDS $\geq$ 13 at booking and pregnancy conditions and events when compared to women with an EPDS $\leq$ 12 (ref category is EPDS < 13) [30]

	OR	AOR	p
Gestational diabetes	1.75 (1.09–2.82)	1.85 (1.14–3.03)	0.01
Assisted reproductive technology	0.50 (0.12–2.07)		
Ante partum haemorrhage	3.39 (1.40–8.23)	2.69 (1.02–7.00)	0.05
Caesarean section	1.08 (0.70–1.66)		
Instrumental delivery	0.94 (0.50–1.78)		
Birth <37 weeks*	1.43 (0.56–3.64)		
Episiotomy	1.16 (0.74–1.81)		
Epidural use	0.95 (0.60–1.51)		
Smoking	1.17 (0.69–2.00)		
Previous pregnancy	1.15 (0.78–1.71)		

*Non-tertiary hospital

medications used to treat depression can also increase the chance of developing diabetes, making it difficult to determine the pathway by which one disease may cause the other.

Potential pathophysiological mechanism underlying depression and diabetes include functional insulin resistant state during major depressive episodes [33]; increased release of catecholamines, growth hormone, glucagon and glucocorticoids [34]; impaired hippocampal neurogenesis (animal studies) [35]; diabetes associated inflammation [34] and decreased plasma brain-deprived neurotrophic factor (BDNF) [3].

Recommendations

More research is needed in order to determine whether mental health issues during pregnancy can be a trigger for GDM during the pregnancy and the chance to developing type 2 diabetes later on in life. There is concern that women who have GDM are often cared for in even more fragmented and medicalised models of care than other pregnant women and this could potentially impact on GDM in a negative way. Research is urgently needed into this question and into models of care that support psychological well-being as well as physical well-being.

Conclusions

It is unclear at this stage as to whether mental health issues, in particular anxiety and depression could be a trigger for the onset of GDM during pregnancy. There is evidence of a bidirectional relationship between diabetes and depression in non-pregnant adults and in women but there has been little investigation into whether this bidirectional relationship also exists for pregnant women who develop GDM. With GDM increasing in the pregnant population, and in some ethnic groups in particular, this needs to be investigated as a matter of urgency. Our recent finding of an association between an EPDS $\geq$ 13 at booking for pregnancy care and the diagnosis of GDM later in the pregnancy supports the importance of undertaking further research. The underlying mechanism for this possible link needs to be established and confirmed in longitudinal studies. Optimal models of care for these women also need to be identified, as currently there is a strong focus on the management of diabetes and not on psychosocial well-being. We concur with Rustad et al. (2011) that the mind/body dualism is a false economy and a team-based approach is needed to address both issues [3].

References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of co-morbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24:1069–78.
2. Ali S, Stone A, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetic Med. 2006;23:1165–73.
3. Rustad JK, Musselman DL, Nemeroff CB. The relationship of depression and diabetes: pathophysiological and treatment implications. Psychoneuroendocrinology. 2011;36:1276–86.
4. Campayo A, de Jonge P, Roy JF, Saz P, de la Camara C, Quintanilla MA, et al. Depressive disorder and incident diabetes mellitus: the effect of characteristics of depression. Am J Psychiatry. 2010;167:580–8.
5. Golden SH, Mariana L, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA. 2008;299:2751–9.
6. Rhee MK, Musselman DL, Ziemer DC, Vaccarino V, Kolm P, Weintraub WS, et al. Unrecognized glucose intolerance is not associated with depression screening for impaired glucose tolerance study 3 SIGT 3. Diabetic Med. 2008;25:1361–5.
7. Mezuk B, Eaton WW, Albrecht MPH, Golden SH. Depression and type II diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008;31:2383–90.
8. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson AE, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. JAMA. 2010;170(21):1884–91.
9. Bowers K, Laughon K, Kim S, Mumford SL, Brite J, Kiely M, et al. The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort in the United States. Paediatr Perinat Epidemiol. 2013;27:323–8.
10. Beucher G. Maternal outcome of gestational diabetes mellitus. Diabetes Metab. 2010;36:522–37.
11. Austin MP, Priest SR, Sullivan EA. Antenatal psychosocial assessment for reducing perinatal mental health morbidity. Cochrane Database Syst Rev. 2008;8(CD005124):2008.
12. Neale A, Wand A. Issues in the evaluation and treatment of anxiety and depression in migrant women in the perinatal period. Australasian Psychiatry. 2013;21(4):379–82.
13. Gotlib IH, Whiffen VE, Mount JH, Milne K, Cordy NI. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol. 1989;57:269–74.
14. Zelkowitz P, Saucier JF, Wang T, et al. Stability and change in depressive symptoms from pregnancy to two months postpartum in childbearing immigrant women. Arch Womens Ment Health. 2008;11:1–11.
15. Collins CH, Zimmerman C, Howard LM. Refugee, asylum seeker, immigrant women and postnatal depression: rates and risk factors. Arch Womens Ment Health. 2011;14:3–11.
16. NSW department of health. NSW health/families NSW supporting families early package—SAFE START In: Health NDo, editor. North Sydney 2009.
17. Rollans M, Schmied V, Kemp L, Meade T. 'We just ask some questions…' theprocess of antenatal psychosocial assessment by midwives. Midwifery. 2013;29:935–42.
18. Cox JL, Holden JM, Sagousky R. Detection of postnatal depression development of the 10 item Edinburgh depression scale. BMJ. 1987;150:782–6.
19. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective.
20. Diabetes Care 2007 ((Suppl 2):S141–S146.).
21. Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: kaiser permanente of colorado gdm screening program. Diabetes Care. 2005;28:579–84.
22. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States (2014), Pregnancy risk assessment monitoring system (PRAMS), 2007–2010. Prev Chronic Dis. 2014;11:130415.
23. Leng J, Shao P, Zhang C, Tian H, Zhang F, Zhang S, et al. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin, China. PLoS One. 2015;10 (e0121029).
24. Carolan M. Gestational diabetes mellitus among women born in South East Asia: a review of the evidence. Midwifery. 2013;Online Feb 2013.
25. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352(24):2477–86.
26. Mocarski M, Savitz DA. Ethnic differences in the association between gestational diabetes and pregnancy outcome. Matern Child Health J. 2012;2:364–73.
27. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the diabetes prevention program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100 (4):1646–53.

28. Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy-induced hypertension. Am J Epidemiol. 2003;158:1148–53.
29. Katon JG, Russo J, Gavin AR, Melville JL, Katon WJ. Diabetes and depression in pregnancy: is there an association? J Womens Health. 2011;20:983–9.
30. Kozhimannil KB, Pereira MA, Harlow BL. Association between diabetes and perinatal depression among low-income mothers. JAMA. 2009;301:842–7.
31. Dahlen HG, Barnett B, Kohlhoff J, Drum ME, Munoz AM, Thronton C. Obstetric and psychosocial risk factors for Australian-born and non-Australian born women and associated pregnancy and birth outcomes: a population based cohort study. BMC Pregnancy and Childbirth. 2015;15(292). doi:10.1186/s12884-015-0681-2.
32. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, et al. Bidirectional association between depression and metabolic syndrome a systematic review and meta-analysis of epidemiological studies. Diabetes Care. 2012;35:1171–80.
33. Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care. 2013;36:480–9.
34. Winokur A, Maislin G, Phillips JL, Amsterdam JD. Insulin resistance after oral glucose tolerance testing in patients with major depression. Am J Psychiatry. 1988;145:325–30.
35. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology biology, and treatment. Biol Psychiatry. 2003;54:317–29.
36. Wang S, Sun Z, Guo Y, Yuan Y, Yang B. Diabetes impairs hippocampal function via advanced glycation end product mediated new neuron generation in animals with diabetes-related depression. Toxicol Sci. 2009;111:72–9.

Part II
The Type 1 Diabetic Mother

Chapter 5
Maternal Overweight and Obesity in Pregnancies Complicated by Type 1 Diabetes

Martina Persson and Bengt Persson

Key Points

- Type 1 diabetes pregnancy is associated with adverse outcomes
- Rates of maternal complications such as pre-eclampsia and caesarean section are increased
- Rates of stillbirth and foetal malformations are increased
- Rates of neonatal complications such as prematurity, low Apgar scores and macrosomia are increased
- The prevalence of maternal overweight and obesity has increased in recent years, markedly so in pregnancies with type 1 diabetes
- The risk of maternal, foetal and perinatal complications in pregnancies with type 1 diabetes increase further with maternal overweight and obesity
- Striving towards normal pre-pregnancy BMI may reduce the risk of adverse pregnancy outcome

Keywords Type 1 diabetes pregnancy · BMI · Caesarean section · Foetal malformations · Prematurity · Foetal macrosomia

Introduction

The marked improvement in the outcome of pregnancies complicated by type 1 diabetes seen in recent years can to a large extent be attributed to improved glycaemic control during pregnancy. However, despite this improvement we are still facing maternal, foetal and neonatal complications that may adversely influence the short- and long-term prognosis for the offspring. These complications include pre-eclampsia, hypertension, perinatal death, malformations, foetal distress, foetal macrosomia, traumatic delivery and neonatal morbidities like respiratory distress, hypoglycaemia and hyperbiliruminemia. The rate of foetal malformations is 3–4 times above normal and represents one of the leading causes of perinatal mortality [1–6].

M. Persson
Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

M. Persson (✉)
Diabetes and Endocrinology, Sachsska Children's Hospital, Sjukhusbacken 10, Stockholm, Sweden
e-mail: Martina.Persson@ki.se

B. Persson
Karolinska Institutet, Stockholm, Sweden
e-mail: bengt.persson@swipnet.se

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_5

During the past few years two additional problems have become increasingly apparent. First, the rate of large for gestational age (LGA) infants has increased markedly and second the proportion of women with obesity during pregnancy has also increased [1, 7–10]. A number of studies have been published on the adverse consequences of maternal overweight and obesity (body mass index >25 kg/m^2) in pregnancies with and without gestational diabetes [11–19]. More than half of maternal deaths in pregnant women without diabetes can directly or indirectly be attributed to maternal overweight/obesity [20]. Maternal overweight and obesity can also lead to increased risks for stillbirth and neonatal and infant death [14, 21]. The incidence of overweight and obesity is increasing also in women with type 1 diabetes [22, 23]. However, maternal obesity in women with type 1 diabetes has so far received little attention [24–27]. The object of this presentation is to discuss in some more detail risks associated with elevated BMI in type 1 pregnancies and possible preventive measures.

Background

Incidence of Type 1 Diabetes and Obesity in Mother and Offspring

The incidence of type 1 diabetes differs significantly between countries and ethnic groups with rates between 0.1–44/100,000 per year. The highest incidence is reported from Finland and Sweden. In Sweden there has been a continuous increase in incidence of type 1 diabetes over the last decades. Type 1 diabetes complicates approximately 0.4% of all pregnancies in Sweden. The incidence of maternal overweight and obesity has also increased worldwide and is now considered one of the most prevalent health concerns in pregnancy. In Sweden, the proportion of women with overweight (BMI > 25 kg/m^2) in early pregnancy has increased from 26% in 1992 to 38% in 2010 [14] in the obstetric population. In the US, 58.5% of women in reproductive age were overweight or obese in 2011–2012 [28] and in the UK 20% of women aged 16–44 years are obese. Similarly, 53 and 43% of pregnant women with type 1 diabetes are overweight or obese in Sweden and Finland respectively [22, 23]. In parallel with increasing incidence of maternal obesity, the frequency of large-for-date infants and neonatal overweight (as expressed by PI ponderal index; defined as birthweight/birth length in cm^3) has increased over time in both pregnancies with and without diabetes [7, 8, 29].

Fat Mass and Its Distribution in Mother and Offspring

Mother

A normal physiological adaption to pregnancy is increased insulin sensitivity in early pregnancy which leads to lipogenesis and accumulation of fat. Fat is stored both subcutaneously in the upper and lower body compartments and as visceral fat. In women with pre-gravid obesity, the proportion of fat stored viscerally is larger than in normal weight women [30]. The increased insulin sensitivity in early pregnancy is replaced by an increasing insulin resistance as pregnancy proceeds. This change in insulin sensitivity facilitates the mobilisation of free fatty acids resulting in a glucose spearing effect in the mother which in turn increases the glucose availability for the foetus. In women without diabetes, there are strong correlations between BMI and fat mass both in the pregnant (early pregnancy, $r^2 = 0.84$) and non-pregnant state ($r^2 = 0.86$) [31].

Offspring

Glucose is the primary source of energy for foetal tissues. Placental transfer of glucose is mediated by facilitated diffusion. The amount of glucose transferred is determined by the maternal–foetal glucose gradient. Glucose is also used for synthesis of foetal lipids, a process stimulated by foetal insulin. Pregnancies with maternal diabetes and/or obesity are characterised by foetal hyperinsulinemia and enhanced foetal lipogenesis [32, 33]. Already at 34 weeks of gestation, foetal fat percentage is twice as high in offspring of type 1 diabetic mothers compared with controls [34]. Offspring of obese mothers with and without diabetes have significantly increased fat mass and amount of intrahepatic fat at birth [35, 36]. Already at birth, girls have significantly more fat and are more insulin resistant than boys [37] in offspring of non-diabetic mothers. Furthermore, foetal macrosomia is more pronounced in female offspring of mothers with type 1 diabetes [7].

Pregnancy Outcome in Women with Type 1 Diabetes and Overweight or Obesity

There is a limited number of studies on the consequences of maternal overweight/obesity for pregnancy outcome in women with type 1 diabetes and these studies are based on rather small numbers of pregnancies. It must be underlined that large sample sizes are required in order to accurately estimate risks of rare outcomes.

Our national study from Sweden covers 3457 singleton births to mothers with type 1 diabetes and 764,498 singleton births to women without diabetes (controls) [22]. 53% of women with type 1 diabetes were overweight or obese in early pregnancy compared with 37% in the control group. Women with type 1 diabetes were more likely to be of Nordic origin, to be smokers and to have a significantly higher prevalence of chronic hypertension. Offspring of mothers with type 1 diabetes had shorter gestational age, were more frequently born preterm and had significantly higher birth weight. The frequency of large-for-date infants (birth weight > 90th percentile in relation to gestational age and sex) was 49% in offspring of mothers with type 1 diabetes compared with 11% in the control group.

The risks for maternal and perinatal complications in relation to maternal early pregnancy BMI were analysed. Maternal outcomes included pre-eclampsia (defined as a blood pressure above 140/90 mmHg after the 20th week of gestation and proteinuria of at least 0.3 g/day) and mode of delivery (emergency or elective Caesarean section). Perinatal outcomes included stillbirth (intrauterine death after 28 weeks of gestation), perinatal mortality (stillbirth and death during the first week of post-natal life), major malformations and foetal macrosomia. Foetal macrosomia was defined as a birth weight or ponderal index above the 90th percentile for sex and gestational age.

Rates for pre-eclampsia, delivery with caesarean section and perinatal complications generally increased with maternal overweight and obesity. The impact of maternal overweight/obesity on the rate of large-for-date infants was more pronounced in offspring of mothers without diabetes. On the other hand, the effect of increasing maternal BMI for the rates of other complications was similar in pregnancies with and without maternal diabetes, Table 5.1.

Maternal obesity in women with type 1 diabetes was associated with a close to 70% higher risk for caesarean section and pre-eclampsia compared with normal weight mothers with type 1 diabetes, Table 5.2. Corresponding increments in risk for major malformations and preterm birth were 77 and 25%, respectively. The already very high frequency of large-for-date infants in pregnancies with type

Table 5.1 Perinatal outcomes for pregnant women with and without type 1 diabetes and stratified by early pregnancy BMI

	BMI 18.5–24.9	BMI 25–29.9	BMI ≥ 30	*p* value*
LGA infant				
Type 1 diabetes	778 [47]	603 [50]	313 [51]	0.170
Non-diabetic	39 265 (8.2)	26 828 [13]	15 049 [18]	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8186 (1.7)	3736 (1.9)	1610 (2.0)	<0.001
Pre-eclampsia				
Type 1 diabetes	222 [14]	185 [15]	114 [18]	0.012
Non-diabetic	9872 (2.1)	6529 (3.3)	4810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 [20]	275 [23]	144 [23]	0.041
Non-diabetic	21 714 (4.5)	9464 (4.7)	4700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Caesarean section				
Type 1 diabetes	748 [46]	639 (53)	362 (59)	<0.001
Non-diabetic	64 131 [13]	34 081 [17]	18 166 [22]	<0.001
Neonatal overweight				
Type 1 diabetes	351 [21]	288 [24]	166 [27]	0.016
Non-diabetic	15 359 [3]	10 430 [5]	6466 [8]	<0.001

Data are presented as numbers (percentages)
*χ^2 test, Kruskal–Wallis test, χ^2 test for trends
BMI, body mass index; LGA, large for gestational age. BMI was measured in the first trimester
*Table is reproduced with permission by BMJ Open

1 diabetes did not further increase with maternal overweight and obesity. However, the proportion of neonatal overweight was 36% higher in offspring of mothers with obesity compared with offspring of normal weight mothers.

A study from Finland, including 881 singleton births to mothers with type 1 diabetes, disclosed an increasing prevalence of maternal overweight and obesity comparing two time periods; 1989–1992 and 2004–2008 [23]. Over the same time periods, maternal glycaemic control in the second half of pregnancy worsened. During the study period, the rates of elective caesarean sections decreased but rates of emergency caesarean section increased. However, mode of delivery was unaffected by maternal BMI. Maternal overweight and obesity was associated with increased risk for admission of the newborn to the neonatal intensive care unit. These findings are in accordance with data from a smaller Canadian study (n = 196 type 1 diabetic pregnancies) [26]. Pregnancies with diabetic nephropathy are usually associated with foetal growth retardation. However, the rate of large-for-date infants is markedly increased in type 1 diabetic pregnancies complicated by maternal obesity and different degrees of nephropathy [25]. In fact, maternal obesity has been demonstrated to be an independent risk factor for large-for-date infants in pregnancies with type 1 diabetes [24]. Also, type 1 diabetes and obesity are likely to act synergistically for the risk of pre-eclampsia, delivery by Caesarean section [26] and major foetal malformations [22].

Table 5.2 Crude and adjusted* ORs; 96% CI for adverse perinatal outcome in pregnant women with T1DM and stratified by early pregnancy BMI

	T1DM		
	BMI 18.5–24.9	BMI 25–29.9	BMI $\geq$ 30
LGA infant			
Crude	1.0	1.13 (0.98–1.32)	1.14 (0.95–1.37)
Adjusted	1.0	1.18 (1.01–1.38)	1.21 (1.00–1.47)
Major malformations			
Crude	1.0	0.93 (0.63–1.37)	1.73 (1.15–2.58)
Adjusted	1.0	0.92 (0.62–1.36)	1.77 (1.18–2.65)
Pre-eclampsia			
Crude	1.0	1.17 (0.95–1.45)	1.45 (1.13–1.86)
Adjusted	1.0	1.21 (0.98–1.50)	1.74 (1.35–2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02–1.47)	1.25 (1.00–1.56)
Adjusted	1.0	1.22 (1.02–1.47)	1.25 (1.00–1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71–3.08)	1.14 (0.44–2.98)
Adjusted	1.0	1.47 (0.70–3.03)	1.08 (0.41–2.83)
Caesarean section			
Crude	1.0	1.38 (1.19–1.60)	1.69 (1.40–2.04)
Adjusted	1.0	1.37 (1.18–1.60)	1.67 (1.38–2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98–1.40)	1.35 (1.09–1.67)
Adjusted	1.0	1.19 (0.99–1.42)	1.36 (1.09–1.69)

Reference group: type 1 diabetic women with normal early pregnancy BMI
*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester and chronic hypertension
BMI, body mass index; LGA, large for gestational age; T1DM, type 1 diabetes. BMI was measured in the first trimester
*Table is reproduced with permission by BMJ Open

Pathophysiological Aspects

Adipose Tissue—Metabolic and Endocrine Functions

The visceral fat mass plays an essential role in the regulation of insulin sensitivity in the body. A large proportion of the amount of circulating free fatty acids (FFA) is released from visceral fat. Free fatty acids, presented to the liver, regulate insulin sensitivity and insulin resistance increases with increasing amount of visceral fat. The visceral fat mass is also an important source of a number of various hormones and inflammatory cytokines. Increased visceral fat mass is associated with marked insulin resistance, lipotoxicity, oxidative stress, endothelial dysfunction, and subclinical inflammation [38]. In pregnancies complicated by obesity, these metabolic alterations may adversely influence placental development and function as well as foetal outcome [30]. Obesity contributes to an exaggerated insulin resistance in pregnancy which in turn leads to elevated maternal glucose levels and increased transfer of glucose to the foetus.

Foetal Hyperglycaemia and Hyperinsulinemia

According to the hypothesis presented by Dr. Jörgen Pedersen in 1952, foetal hyperglycaemia leads to stimulation of the foetal beta cells and foetal hyperinsulinemia. This hypothesis has been confirmed in the large "HAPO" study (Hyperglycemia adverse pregnancy outcome) demonstrating a linear association between increasing maternal glucose values and foetal hyperinsulinemia measured as C-peptide concentrations >90th percentile in cord blood [32]. This study also reported an independent association between maternal BMI and foetal hyperinsulinemia [39]. Foetal insulin plays a major role in the regulation of foetal growth. Already modestly increased levels of maternal glucose stimulate foetal insulin secretion [32]. Excess insulin levels in the foetus leads to enhanced growth and risk of foetal macrosomia. In experimental studies it has been demonstrated that foetal hyperinsulinemia is a predisposing factor for foetal hypoxia [40]. Hypoxia stimulates the production of erythropoietin which in turn enhances erytropoesis. In offspring of mothers with type 1 diabetes, levels of erythropoietin in cord blood are strongly correlated to maternal glycaemic control [41]. Maternal diabetes and obesity may independently of each other contribute to foetal hyperinsulinemia and chronic foetal hypoxia. Furthermore, foetal macrosomia per se increases the risk for traumatic delivery and foetal hypoxia. As opposed to normal weight women, women with overweight or obesity are insulin resistant already in early pregnancy. This may lead to exposure of the embryo to high levels of glucose which may have teratogenic effect and increased risk of spontaneous abortion and foetal malformations. Based on experimental data, it has also been hypothesised that hyperinsulinemia during foetal life may lead to malprogramming of neuroendocrine networks with adverse metabolic consequences for the offspring [42] (Fig. 5.1).

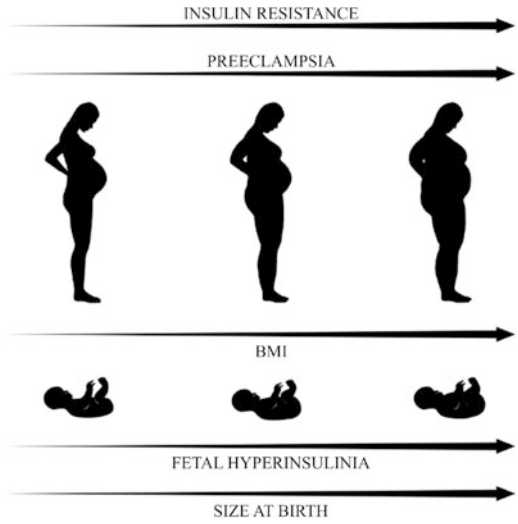


Fig. 5.1 This figure illustrates that increasing maternal BMI is associated with increasing risks of maternal and foetal hyperinsulinemia, pre-eclampsia and foetal macrosomia. Illustration by Emil Mogensen, reprinted with permission

Other Possible Contributing Factors to Pregnancy Complications

Factors that may contribute to poor outcome in pregnancies with both maternal type 1 diabetes and obesity include differences in socioeconomic factors, diet, physical activity, smoking habits and alcohol use as well as prevalence of comorbidities like chronic hypertension. It has also been proposed that alterations in the gut microbiome in women with diabetes and/or obesity may increase risks for pregnancy complications [43]. It was also recently demonstrated that the placenta has its own microbiome with potential impact on risks for pregnancy complications [44]. Cord coiling and labour dystocia are more frequently seen in obese pregnancies and may contribute to adverse outcome.

Recommendations and Guidelines

Preventive Measures

Adolescents

Eating disorders and obesity are frequently seen in adolescent and young adult girls with type 1 diabetes [45, 46] and correlate with poor glycaemic control [46]. This group of young females needs strong psychosocial support and advice on a healthy lifestyle. Special attention should be paid to improve dietary habits and glycaemic control and to strive for a normal BMI. In order to improve the outlook for this group, a well-functioning team of physicians, diabetes nurses, social workers, psychologists and dieticians are needed. Pre-pregnancy counselling should be introduced already during adolescence, please see below.

Pre-pregnancy Counselling

Pre-pregnancy counselling should be given already during adolescence and be repeated at regular intervals thereafter. This counselling includes general information on the risks of pregnancy, the importance of birth control, genetic counselling and of maintaining blood glucose levels as close to normal as possible. The importance of trying to obtain a normal body weight should be stressed; all possible support should be given to reach this goal. The motivation to follow this advice should be strong in view of the great reproductive value of a normal pre-pregnancy BMI. Women and their partners who are contemplating pregnancy in the near future should receive education on the importance of intensive management of diabetes, the need of frequent outpatients' visits to obstetrician and endocrinologist of pregnancy.

Gestational Weight Gain

Gestational weight gain is inversely correlated to pre-pregnancy BMI [47] but a majority of women with overweight or obesity in early pregnancy gain weight in excess of what is recommended in the IOM (Institute of Medicine) guidelines [48]. According the IOM guidelines from 2009, pregnancy weight gain for women with overweight (BMI 25–29.9) and obesity (BMI $\geq$ 30) should not exceed 11.9 and 9 kg, respectively. Pre-pregnancy overweight/obesity is a stronger predictor of adverse pregnancy outcome than abnormal gestational weight gain. Trials of lifestyle interventions in obese pregnancies have demonstrated little effect on the risk of poor pregnancy outcome [49]. In a recent

RCT from the UK, obese pregnant women were randomised to standardised antenatal care or an intervention programme including dietary advice and physical activity. The diet consisted of food with low glycaemic index and low content of saturated fat. The intervention resulted in a lower gestational weight gain but had no significant effect on the risks for gestational diabetes or large-for-date infants [50]. It is possible that the limited success from intervention studies on obesity in pregnancy is partly explained by an early metabolic programming which reduces effects of changes in diet and physical activity [51].

It is important to be aware of potential problems with caloric restriction during pregnancy in women with type 1 diabetes. The metabolic goal is to obtain a glucose level as close to normal as possible (fasting blood glucose 4–5 mmol/l and postprandial 6–7 mmol/l) and to avoid hypoglycaemia. In early pregnancy, the risk for hypoglycaemia is increased as a result of increased insulin sensitivity. Tight blood glucose control increases risk for hypoglycaemia unawareness which must be avoided. All pregnant women with type 1 diabetes and their partners should be aware of the increased risk for nocturnal hypoglycaemia. Characteristic for the metabolism of pregnant women is that even a short period of starvation leads to a rapid development of ketonemia. Against this background, attempts to reduce the caloric intake in order to lose weight should be avoided in women with type 1 diabetes. In order to minimise great fluctuations in blood glucose the caloric intake should be divided in several smaller meals (i.e. breakfast, snack, lunch, snack, dinner and snack).

Conclusion

It is evident that maternal overweight and obesity are associated with much increased risk for adverse pregnancy outcome. These serious short- and long-term consequences occur even if the glycemic control during pregnancy is appropriate. Against this background it is alarming that the incidence of maternal obesity is increasing. Preventive measures must therefore focus both on trying to obtain a normal pre-pregnancy BMI and normoglycaemia during pregnancy. Pre-pregnancy counselling, emphasising the reproductive value of a normal pre-pregnancy BMI, should be offered at regular intervals starting already during adolescence. All efforts should be made to close the gap between existing knowledge and its application.

References

1. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diab Care. 2009;32(11):2005–9 Epub 2009/08/14.
2. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ (Clinical research ed). 2006;333(7560):177. Epub 2006/06/20.
3. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ (Clinical research ed). 2004;328(7445):915. Epub 2004/04/07.
4. Colstrup M, Mathiesen ER, Damm P, Jensen DM, Ringholm L. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications? The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26 (17):1682–6. Epub 2013/04/11.
5. Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. White's classification and pregnancy outcome in women with type 1 diabetes: a population-based cohort study. Diabetologia. 2015. Epub 2015/10/18.
6. Tennant PW, Glinianaia SV, Bilous RW, Rankin J, Bell R. Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. Diabetologia. 2014;57(2):285–94 Epub 2013/12/03.

7. Persson M, Pasupathy D, Hanson U, Norman M. Birth size distribution in 3,705 infants born to mothers with type 1 diabetes: a population-based study. Diab Care. 2011;34(5):1145–9 Epub 2011/03/25.
8. Hanson U, Persson B. Outcome of pregnancies complicated by type 1 insulin-dependent diabetes in Sweden: acute pregnancy complications, neonatal mortality and morbidity. Am J Perinatol. 1993;10(4):330–3 Epub 1993/07/01.
9. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003–2009. Prev Med. 2013;56(6):372–8 Epub 2013/03/05.
10. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2014;384(9945):766–81. Epub 2014/06/02.
11. Persson M, Johansson S, Villamor E, Cnattingius S. Maternal overweight and obesity and risks of severe birth-asphyxia-related complications in term infants: a population-based cohort study in Sweden. PLoS medicine. 2014;11(5):e1001648. Epub 2014/05/23.
12. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, et al. Maternal obesity and risk of preterm delivery. JAMA. 2013;309(22):2362–70 Epub 2013/06/13.
13. Heslehurst N, Simpson H, Ells LJ, Rankin J, Wilkinson J, Lang R, et al. The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis. Obes Rev: An Official J Int Assoc Study Obes. 2008;9(6):635–83 Epub 2008/08/05.
14. Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. BMJ (Clinical research ed). 2014;349:g6572 Epub 2014/12/04.
15. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diab Care. 2012;35(4):780–6 Epub 2012/02/24.
16. Langer O, Yogev Y, Xenakis EM, Brustman L. Overweight and obese in gestational diabetes: the impact on pregnancy outcome. Am J Obstet Gynecol. 2005;192(6):1768–76 Epub 2005/06/23.
17. Roman AS, Rebarber A, Fox NS, Klauser CK, Istwan N, Rhea D, et al. The effect of maternal obesity on pregnancy outcomes in women with gestational diabetes. J Mater-fetal & Neonatal Med: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2011;24(5):723-7. Epub 2011/03/04.
18. Yogev Y, Langer O. Pregnancy outcome in obese and morbidly obese gestational diabetic women. Eur J Obstet Gynecol Reprod Biol. 2008;137(1):21–6 Epub 2007/05/23.
19. Ben-Haroush A, Hadar E, Chen R, Hod M, Yogev Y. Maternal obesity is a major risk factor for large-for-gestational-infants in pregnancies complicated by gestational diabetes. Arch Gynecol Obstet. 2009;279 (4):539–43 Epub 2008/09/02.
20. Confidential Enquiry into Maternal and Child Health. Pregnancy in women with Type 1 and Type 2 diabetes 2002–2003 E. CEMACH, London: Wales and Northern Ireland; 2005.
21. Carmichael SL, Blumenfeld YJ, Mayo J, Wei E, Gould JB, Stevenson DK, et al. Prepregnancy Obesity and Risks of Stillbirth. PloS one. 2015;10(10):e0138549. Epub 2015/10/16.
22. Persson M, Pasupathy D, Hanson U, Westgren M, Norman M. Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study. BMJ Open. 2012;2(1):e000601. Epub 2012/02/16.
23. Klemetti M, Nuutila M, Tikkanen M, Kari MA, Hiilesmaa V, Teramo K. Trends in maternal BMI, glycaemic control and perinatal outcome among type 1 diabetic pregnant women in 1989–2008. Diabetologia. 2012;55 (9):2327–34 Epub 2012/07/04.
24. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol. 2004;191(3):964–8 Epub 2004/10/07.
25. Yogev Y, Chen R, Ben-Haroush A, Hod M, Bar J. Maternal overweight and pregnancy outcome in women with Type-1 diabetes mellitus and different degrees of nephropathy. J Matern-Fetal & Neonatal Med: The Official J Eur Assoc Perinat Med Fed Asia and Oceania Perinat Soc Int Soc Perinat Obstet. 2010;23(9):999–1003 Epub 2010/01/12.
26. Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. Diabetes Endocrine Pregnancy Outcome Study in Toronto. QJM: Monthly J Ass Phys. 2001;94(7):347–56. Epub 2001/07/04.
27. Handisurya A, Bancher-Todesca D, Schober E, Klein K, Tobler K, Schneider B, et al. Risk factor profile and pregnancy outcome in women with type 1 and type 2 diabetes mellitus. Journal of women's health (2002). 2011;20 (2):263–71. Epub 2011/01/12.
28. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS data brief. 2015;219:1–8 Epub 2015/12/04.

29. Kramer MS, Morin I, Yang H, Platt RW, Usher R, McNamara H, et al. Why are babies getting bigger? Temporal trends in fetal growth and its determinants. J pediatr. 2002;141(4):538–42 Epub 2002/10/16.
30. Jarvie E, Hauguel-de-Mouzon S, Nelson SM, Sattar N, Catalano PM, Freeman DJ. Lipotoxicity in obese pregnancy and its potential role in adverse pregnancy outcome and obesity in the offspring. Clin Sci (Lond). 2010;119 (3):123–9 Epub 2010/05/07.
31. Sewell MF, Huston-Presley L, Amini SB, Catalano PM. Body mass index: a true indicator of body fat in obese gravidas. J Reprod Med. 2007;52(10):907–11 Epub 2007/11/06.
32. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. New Engl J Med. 2008;358(19):1991–2002 Epub 2008/05/09.
33. Persson B. Assesment of metabolic control in diabetic pregnancy. Ciba Foundation Symposium: Ciba Foundation Symposium, Elsevier; 1974. p. 274.
34. Anblagan D, Deshpande R, Jones NW, Costigan C, Bugg G, Raine-Fenning N, et al. Measurement of fetal fat in utero in normal and diabetic pregnancies using magnetic resonance imaging. Ultrasound in Obstet Gynecol: The Official J Int Soc Ultrasound Obstet Gynecol. 2013;42(3):335–40 Epub 2013/01/05.
35. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol. 2006;195(4):1100–3 Epub 2006/08/01.
36. Brumbaugh DE, Tearse P, Cree-Green M, Fenton LZ, Brown M, Scherzinger A, et al. Intrahepatic fat is increased in the neonatal offspring of obese women with gestational diabetes. J Pediatr. 2013;162(5):930–6 e1. Epub 2012/12/25.
37. Shields BM, Knight B, Hopper H, Hill A, Powell RJ, Hattersley AT, et al. Measurement of cord insulin and insulin-related peptides suggests that girls are more insulin resistant than boys at birth. Diab Care. 2007;30 (10):2661–6 Epub 2007/05/04.
38. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol: JASN. 2004;15(11):2792–800 Epub 2004/10/27.
39. Hyperglycaemia and Adverse Pregnancy Outcome. (HAPO) Study: associations with maternal body mass index. BJOG: An Int j obstet Gynaecol. 2010;117(5):575–84 Epub 2010/01/22.
40. Philipps AF, Widness JA, Garcia JF, Raye JR, Schwartz R. Erythropoietin elevation in the chronically hyperglycemic fetal lamb. Proc Soc Exp Biol Med. 1982;170(1):42–7 Epub 1982/05/01.
41. Widness JA, Teramo KA, Clemons GK, Voutilainen P, Stenman UH, McKinlay SM, et al. Direct relationship of antepartum glucose control and fetal erythropoietin in human type 1 (insulin-dependent) diabetic pregnancy. Diabetologia. 1990;33(6):378–83 Epub 1990/06/01.
42. Plagemann A. Maternal diabetes and perinatal programming. Early Human Dev. 2011;87(11):743–7 Epub 2011/09/29.
43. Miele L, Giorgio V, Alberelli MA, De Candia E, Gasbarrini A, Grieco A. Impact of Gut Microbiota on Obesity, Diabetes, and Cardiovascular Disease Risk. Curr Cardiol Rep. 2015;17(12):120. Epub 2015/10/27.
44. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014;6(237):237ra65. Epub 2014/05/23.
45. Colton P, Olmsted M, Daneman D, Rydall A, Rodin G. Disturbed eating behavior and eating disorders in preteen and early teenage girls with type 1 diabetes: a case-controlled study. Diab Care. 2004;27(7):1654–9 Epub 2004/06/29.
46. Domargard A, Sarnblad S, Kroon M, Karlsson I, Skeppner G, Aman J. Increased prevalence of overweight in adolescent girls with type 1 diabetes mellitus. Acta Paediatrica (Oslo, Norway: 1992). 1999;88(11):1223–8. Epub 1999/12/11.
47. Chu SY, Callaghan WM, Bish CL, D'Angelo D. Gestational weight gain by body mass index among US women delivering live births, 2004–2005: fueling future obesity. Am J Obstet Gynecol. 2009;200(3):271 e1–7. Epub 2009/01/13.
48. Rasmussen KM, Abrams B, Bodnar LM, Butte NF, Catalano PM. Maria Siega-Riz A. Recommendations for weight gain during pregnancy in the context of the obesity epidemic. Obstet Gynecol. 2010;116(5):1191–5 Epub 2010/10/23.
49. Ruifrok AE, van Poppel MN, van Wely M, Rogozinska E, Khan KS, de Groot CJ, et al. Association between weight gain during pregnancy and pregnancy outcomes after dietary and lifestyle interventions: a meta-analysis. Am J Perinatol. 2014;31(5):353–64 Epub 2013/08/07.
50. Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, et al. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. Lancet Diab Endocrinol. 2015;3 (10):767–77 Epub 2015/07/15.
51. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. Int J Obes (2005). 2015;39(4):642–9. Epub 2015/03/18.

Chapter 6
Glycemic Control and Insulin in Type 1 Diabetic Pregnancies

Eftychia Koukkou and Ioannis Ilias

Key Points
Pregnancy in a woman with Type 1 Diabetes Mellitus (DM1)

- Is a high-risk pregnancy
- If uncontrolled glycemia:
  - Cardiovascular malformations
  - Neural tube defects
  - Urinary tract malformations
- No clear cutoff in relationship between maternal A1C and risk for congenital abnormalities
- Women with DM1 during pregnancy should be followed in organized centers
- Frequent outpatient office visits every one to two weeks are necessary
- Measurement of A1C should be repeated every month, targeting at 6.0–6.5% (42–48 mmol/mol)
- Glycemia monitoring is imperative (self-monitoring of blood glucose or continuous glucose monitoring)
- Newer insulin analogues and insulin pumps offer more flexibility in treatment
- A vaginal birth is preferable to a cesarean birth

Keywords Blood glucose · Female · Humans · Hyperglycemia · Pregnancy · Pregnancy in diabetics · Diabetes mellitus · Type 1

Abbreviations

DM1	Type 1 Diabetes Mellitus
SMBG	Self-monitoring of blood glucose
CGM	Continuous glucose monitoring
NPH	Neutral protamine Hagedorn
A1C	Hemoglobin A1c
FBG	Fasting blood glucose
CB	Cesarean birth
ADA	American Diabetes Association
BMI	Body mass index
CSII	Continuous subcutaneous insulin infusion

E. Koukkou (✉) · I. Ilias
Endocrine Unit, Elena Venizelou Hospital, 2, El Venizelou Sq, 11521 Athens, GR, Greece
e-mail: ekoukkou@gmail.com

I. Ilias
e-mail: iiliasmd@yahoo.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_6

DKA Diabetic ketoacidosis
IGF-1 Insulin-like growth factor I
FDA United States Food and Drug Administration

Introduction—Importance of Good Glycemic Control

Pregnancy in a woman with Type 1 Diabetes Mellitus (DM1) is a high-risk pregnancy, because DM1 poses problems before and during pregnancy [1], and at the same time the physiological adaptations of pregnancy can affect the natural history of the diabetes and the diabetic complication, which may already exist. Hyperglycemia is detrimental to the fetus [2, 3]. A fivefold increase in the rate of cardiovascular malformations and a more than twofold increase in the rate of neural tube defects and urinary malformations have been noted [4, 5]. For pregnant women with diabetes the risk for the latter abnormalities remains slightly higher than in the general population even if hemoglobin A1c (A1C) is within normal levels [6]. There is no clear cutoff in the relationship between the maternal A1C and the risk for congenital abnormalities [7]. However, if A1C is higher than 10% upon conception, the risk of birth defects is approximately 22% [8]. Furthermore, the presence of congenital abnormalities is associated with increased risk of perinatal mortality [1]. At the other end of the spectrum, hypoglycemia can also be dangerous, as pregnancy losses are reported to be increased at both the extremes of glycemia [9]. Also, hypoglycemia may interfere with normal fetal cardiogenesis and brain development [10, 11]. Since good diabetic control is of outmost importance at the beginning of pregnancy, the treating physician should discuss at regular intervals with women with DM1 of reproductive age their intention of pregnancy and highlight the need for planned pregnancy by informing them on the potential risks to the fetus of unsatisfactory glycemia before conception [12]. In the planning stages of pregnancy glycemic targets should be as close to normal as possible: pre-meal glucose values between 70 and 100 mg/dL, postprandial glucose values between 90 and 140 mg/dL, and A1C within the upper limit of normal.

Monitoring Blood Glucose Levels—Defining Glycemic Control

Following-up of women with DM1 during pregnancy should be done in organized centers, capable of providing diabetes care as well as obstetric and neonatal care [13]. Frequent outpatient office visits every 1 to 2 weeks are required for close monitoring of maternal glycemia. Glucose metabolism is altered during pregnancy due to the insulin-independent glucose uptake by the placenta and the "diabetogenic" effect of the placental hormones. Blood glucose levels during pregnancy are overall about 10% lower compared to levels in non-pregnant subjects. Hernandez et al. [14] analyzed the data from 12 studies published between 1975 and 2008, with a total of 255 pregnant women with normal weight and glucose tolerance, with mean gestational age at the study time 33.8 ± 2.3 weeks (range 24–40.8 ± 0.09–8.1 weeks). They report that on average, fasting blood glucose (FBG) was 70.9 ± 8 mg/dL, while 1 and 2 h post prandial were 109 ± 13 and 88 ± 10 mg/dL respectively and mean 24 h BG 88 ± 10 ng/dL.

Ideally, the treatment goal in pregnancies complicated by diabetes is to mimic the glycemia in normal pregnancy [15]. The glycemic targets during pregnancy may vary from fasting levels of 60–105 mg/dL to postprandially 130–155 mg/dL (after one hour) or 120–130 (after two hours)

according to the authority [16–21]. By adopting not too strict but also not too loose glycemic levels, a significant reduction of neonatal macrosomia is achieved without a significant increase in the incidence of underweight newborns [16–20]. A very loose glycemic control (with a fasting blood glucose over 126 mg/dL is to be avoided at all cost (it is associated with increased pre-eclampsia, increased rate of cesarean birth (CB) and birth weights greater than the 90th centile) [3, 22] (Tables 6.1 and 6.2).

Self-monitoring of blood glucose (SMBG) 6–7 times daily (including pre-meal and postprandial values) is mandatory; a further measurement between 02:00 and 04:00 may be needed for detection of possible nocturnal hypoglycemia. Many experts recommend postprandial SMBG one hour after meals (considered to be the highest observed), however, since in non-pregnant subjects with DM1 postprandial SMBG is usually done 2 hours after meals it may be more convenient to continue to do so in pregnancy [23]. The optimal postprandial time for testing is not clearly defined. Buhling et al. used a continuous glucose monitoring (CGM) system and found that the optimal timing is between 45 and 120 min postprandial, and they suggested that measurements should be done 60 min post meal because this can be more easily calculated and offers more freedom to eat the recommended number of snacks [24].

The current gold standard marker for glycemic control is A1C (reflecting blood glucose fluctuations over the previous 2–3 months). However, A1C levels fall during the normal pregnancy due to the increased red blood cell turn over and are also affected by the abnormal erythrocyte life span, which characterizes the iron deficiency anemia, a common finding in pregnancy [25, 26]. Therefore the measurement of A1C should be repeated every month of the gestation [27] and trimester-specific normal targets should be used. A target of 6.0–6.5% (42–48 mmol/mol) is recommended but 6.0% (42 mmol/mol) may be optimal as pregnancy progresses [28]. It should be noted that an A1C level lower than 6.0% may imply repeated hypoglycemic episodes, which may be detrimental to the fetus (and particularly its cardiac development) [9, 10, 17] (Table 6.2).

Any treatment modality in patients with DM1 can be assessed with CGM. Although CGM can delineate the variability in glycemic levels and pinpoint extremes that are to be avoided in pregnancy there is still uncertainty in its utility in pregnancy. Further studies are warranted and addition of affordable CGM in closed-loop insulin sensing and delivery systems may be used in the future [23, 29–32].

In any case, optimal control should be achieved safely, that is without the fear of hypoglycemia, especially in women with a history of long-standing diabetes with severe hypoglycemias or a history of hypoglycemia unawareness. In these cases the American Diabetes Association (ADA) suggests "less stringent targets based on clinical experience and individualization of care" [28].

Table 6.1 Glycemic targets in type 1 diabetic pregnancies: *as close to normal as possible*

• Pre-meal glucose values: 70–100 mg/dL
• Postprandial glucose values: 90–140 mg/dL
• A1C: within the upper limit of normal

Table 6.2 Monitoring of blood glucose levels in pregnant women with DM1

• Frequent outpatient office visits: every 1–2 weeks
• Glycemic targets during pregnancy may vary
– Fasting levels: 60–105 mg/dL
– Postprandial levels: 130–155 mg/dL (+1 h) or 120–130 (+2 h)
• Loose glycemic control (= fasting blood glucose > 126 mg/dL): *to be avoided*
• Self-monitoring of blood glucose (SMBG): 6–7 x/day
• A1C: every month of pregnancy—target: 6.0–6.5% (42–48 mmol/mol)

Nutrition and Exercise

During pregnancy sufficient caloric intake spread over three meals and three snacks is recommended. Particularly the bedtime snack should never be omitted. The proposed nutrition composition is 35–45% carbohydrates, with a minimum intake of 175 g carbohydrate daily, 20–25% protein and 30–40% fat [33, 34]. Recommended weight gain during pregnancy according to the pre-pregnancy body mass index (BMI) is presented in Table 6.3 [33].

Physical activity is encouraged during pregnancy due to its effect on limiting excess weight gain, on improving the pregnancy-induced insulin resistance and lessening of the delivery-related complications [35, 36]. The American College of Obstetricians and Gynecologists recommends at least 30 min of moderate intensity exercise on most days of the week in healthy pregnant women [37].

Although the beneficial effect of exercise on the glycemic control in T1 diabetic pregnancies was questioned because of the increased risk of hypoglycemia and the increased caloric intake in order to prevent it [38], it appears that a 20 min walk after meals, which is both gestationally appropriate and practical, along with a controlled diet may assist these women in achieving optimal glucose control during pregnancy [39].

Available Insulins for Pregnancy

Intensified insulin regimens are followed in pregnancy, either with multiple injections (basal and prandial) or continuous subcutaneous insulin infusion (CSII; insulin pump) [40]. It should be noted that insulin requirements vary considerably during pregnancy and that they also differ from person to person. At the end of the first trimester, particularly overnight, there is a frequent risk of hypoglycemia; therefore a reduction of administered insulin may be needed. Later on, owing to insulin resistance, insulin requirements increase gradually from the second trimester until the 32nd to 34th week, when insulin requirements stabilize or are even slightly reduced until parturition [41].

Women with DM1 should hone their skills to adjust dosages of fast-acting insulin/insulin analogues on the basis of SMBG, food intake, and physical activity. The immediate family should be educated on the use of glucagon for the prompt treatment of severe hypoglycemia. Diabetic ketoacidosis (DKA) can occur in diabetic pregnancy, especially when DM1 is diagnosed in pregnancy or if CSII fails. The treatment of DKA in pregnant subjects is the same as in non-pregnant subjects; it should be noted that it may have adverse effects on the fetus. In case where corticosteroid administration is deemed necessary to facilitate fetal pulmonary maturation, an increase of at least 50% of the administered insulin doses for 72 h—followed by a gradual decrease—is necessary; this should be combined with close monitoring of glucose values.

Although regular and isophane/NPH human insulins were the mainstay of insulin treatment of subjects with DM1 (and are still considered class A drugs by the FDA, i.e. that adequate and well-controlled studies have not demonstrated a risk to the fetus), their use has been superseded by the newer insulin analogues. Insulin analogues used in pregnancy are the ultrarapid-acting lispro and aspart, and the slow-acting analogues, detemir and glargine [42, 43]. There are no data on glulisine and degludec use in pregnancy [42, 46] and they are not licensed for pregnancy.

Table 6.3 Weight gain during pregnancy

• *according to the pre-pregnancy body mass index* (*BMI*)
– for BMI < 19.8 kg/m^2: (+)12.5–18.0 kg
– for BMI: 19.8–26 kg/m^2: (+) 11.2–15.7 kg
– for BMI > 26 kg/m^2: (+) 6.7–11.2 kg

Insulin Lispro

Lispro has been available for 20 years and there is already enough experience on its use. It has not been associated with an increased rate of birth defects in newborns. In vitro and in vivo studies have shown that it does not cross the placenta. Also there is no difference in the production of anti-insulin antibodies, both in non-pregnant and pregnant subjects. In vitro studies showed 1.5 times higher binding of lispro with the IGF-1 receptor compared to human insulin [44], which however, appears to be devoid of clinical significance and no adverse effect of lispro on the development of diabetic retinopathy in pregnancy has been noted [43]. Its use in pregnancy is a safe and flexible treatment option, with good results in terms of metabolic control and low rates of hypoglycemic episodes [42, 45]. The FDA has approved its use in pregnancy (as a class B drug, i.e. that animal studies have failed to demonstrate a risk to the fetus but there are no adequate studies in pregnant women) [46]. The concentrated form of lispro (Humalog U200), which has been recently launched in the market, as it is bioequivalent to lispro U100, is also permitted and used in pregnancy [47].

Insulin Aspart

Aspart does not cross the placenta and shows similar production of anti-insulin antibodies to human insulin. In vitro studies have shown that the binding of aspart with the insulin-like growth factor I (IGF-1) receptor is lower by 69% compared to the corresponding connection of human insulin [43]. It has no adverse effects on the progression of diabetic retinopathy, fetal congenital malformations, or maternal and neonatal morbidity [42]. It may lead to less nocturnal hypoglycemia compared to regular insulin. Aspart has received approval from the FDA and the European Medicines Agency for use in pregnancy (also as a class B drug) [46].

Insulin Detemir

In a recent randomized study in pregnant women with type 1 diabetes insulin detemir was not proved inferior to NPH insulin [51]. Moreover, it was shown that treatment with insulin detemir resulted in similar rates of early fetal loss and perinatal deaths and a more favorable gestational age at birth compared with NPH insulin [52]. Animal studies with detemir for toxicity and teratogenicity have also been negative. No differences versus NPH insulin in the incidence of congenital abnormalities, perinatal deaths, percentage of large-for gestational age babies, or neonatal hypoglycemia have been shown [42, 46], and it was recently shown that detemir does not cross the human placenta. Detemir has been cleared for use in pregnancy by the FDA (as a class B drug).

Insulin Glargine

Administration of glargine in animals did not cause birth defects in fetuses. It has high affinity for the human IGF-1 receptor (leading to theoretical concerns of macrosomia if used in pregnancy) [48, 49]. In less robust studies no significant differences in the rates of maternal/neonatal morbidity or macrosomia rates compared to NPH have been noted, leading to an FDA categorization of a class C

drug in pregnancy (i.e., absence of adequate and well-controlled studies in humans, although potential benefits may warrant use of the drug in pregnant women despite potential risks) [42, 46]. However, in a recent meta-analysis, eight studies of women using glargine (n = 331) or NPH (n = 371), published between 2007 and 2010, were analyzed and no significant differences in the efficacy and safety-related outcomes were found between glargine and NPH use during pregnancy [50]. Thus, the use of glargine may be considered during pregnancy, if necessary [46].

CSII (Insulin Pumps) Pros and Cons

The use of CSII in pregnancy has led many researchers to conclude that it is an acceptable and equally effective method of achieving euglycemia during pregnancy compared with multiple injections [53–56] (Table 6.4), although there are dissenting voices from some specialists who think that it is associated with greater risk of diabetic ketoacidosis and neonatal hypoglycemia [57, 58]. The benefits of CSII include greater flexibility in physical activity and planning meals [59]. Furthermore, the implementation of multiple infusion rates prevents nocturnal hypoglycemia and fasting hyperglycemia (dawn phenomenon); the absorption and the action of insulin with CSII are more predictable. Nevertheless, a high level of self-motivation and some skill are required of the patient to use the pump; poor compliance is more likely to lead to complications [56]. Treating physicians need also to be familiarized with CSII; it is an expensive treatment option and less-widely available compared to multiple injections.

Ideally CSII should be started at least 3 months before conception so that the patient with DM1 can be familiarized with it. The use of CSII in pregnancy is not different to the use in non-pregnant subjects. However, certain points should be emphasized; first, the belly area should be avoided for the insertion of the infusion catheter, because of the skin distention as pregnancy progresses. Second, due to changes in insulin sensitivity as pregnancy progresses, it is pertinent that the insulin to carbohydrate ratio, as well as the insulin sensitivity index and the correction boluses are adjusted appropriately [60].

Table 6.4 CSII (insulin pumps)*: pros (+) and cons (−)

(+) greater flexibility in physical activity
(+) greater flexibility in planning meals
(+) prevents nocturnal hypoglycemia
(+) prevents fasting hyperglycemia (dawn phenomenon)
(−) high level of self-motivation
(−) patients' skill required for its use
(−) poor compliance is more likely to lead to complications

*Ideally should be started >3 months before conception

Delivery

To avoid complications such as stillbirth, macrosomia, or iatrogenic prematurity ideally the pregnant woman with DM1 should give birth by the 38th week of pregnancy. A vaginal birth is preferable [61]; CB entails a higher risk compared to vaginal birth of wound infection in subjects with diabetes. Although CB eliminates the chance of shoulder dystocia, there is still no conclusive evidence that it eliminates the risk of brachial plexus injury [62]. Moreover, some studies suggest that CB increases the likelihood of DM1 in the offspring [63–65]. During childbirth insulin should be given with an IV insulin infusion according to blood glucose measurements. The goal is to maintain blood glucose close to normal in order to reduce the risk of neonatal hypoglycemia and to sustain sufficient fetal oxygen supply [66]. The insulin infusion rate should be halved immediately after birth [67]. The use of CSII is also possible during vaginal delivery provided that a person familiar with CSII is present at all times in the delivery room.

Conclusions

Pregnancy in T1DM women is a high-risk pregnancy, especially in long-standing diabetes, therefore, the follow-up should be done in organized centers and with frequent outpatient office visits. The measurement of A1C should be repeated every month, targeting at 6.0–6.5% and glycemia monitoring with either SMBG or CGM is imperative. The newer insulin analogues and CSII offer more flexibility in treatment and the insulin dose should be adjusted as needed. A vaginal birth at term should be aimed to, unless there are obstetric complications.

Recommendations and Guidelines

In the planning stages of pregnancy glycemic targets should be pursued as close to normal as possible: pre-meal glucose values between 70 and 100 mg/dL; postprandial glucose values between 90 and 140 mg/dL and A1C within the upper limit of normal. Follow-up of women with DM1 during pregnancy should be done in organized centers with frequent outpatient office visits every one to two weeks. Weight gain during pregnancy should be modest and according to the pre-pregnancy body mass index (BMI). Retinal assessment should be done with the confirmation of pregnancy and at 16–20 weeks of gestation—or sooner, if necessary. Measurement of A1C should be repeated every month, targeting at 6.0–6.5% (42–48 mmol/mol). Glycemic targets during pregnancy (measurements 6–7 times daily): fasting levels: 60–105 mg/dL; postprandially: 130–155 mg/dL (after one hour) or 120–130 (after two hours). Insulin treatment should be pursued with regular and isophane/NPH human insulins or—better—with newer insulin analogues (ultrarapid-acting lispro and aspart, and the slow-acting analogues, detemir and—if necessary—glargine). Delivery by the 38th week of pregnancy with a vaginal birth is preferable to a caesarean section.

References

1. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diabetes Care. 2009;32:2005–9.
2. Murphy HR. Diabetes and pregnancy. Diab Med. 2014;31(3):251.

3. Middleton P, Crowther CA, Simmonds L. Different intensities of glycaemic control for pregnant women with pre-existing diabetes. Cochrane Database Syst Rev. 2012;8:CD008540.
4. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. Obstet Gynecol Surv. 1986;41:325–35.
5. Jensen DM, Korsholm L, Ovesen P, Beck-Nielsen H, Moelsted-Pedersen L, Westergaard JG, et al. Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. Diabetes Care. 2009;32(6):1046–8.
6. Colstrup M, Mathiesen ER, Damm P, Jensen DM, Ringholm L. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications? J Matern Fetal Neonatal Med. 2013;26(17):1682–6.
7. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. Diabetes Care. 2007;30:1920–5.
8. Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. Am J Obstet Gynecol. 1987;156(5):1096–100.
9. Jovanovic L, Knopp RH, Kim H, Cefalu WT, Zhu XD, Lee YJ, et al. Elevated pregnancy losses at high and low extremes of maternal glucose in early normal and diabetic pregnancy: evidence for a protective adaptation in diabetes. Diabetes Care. 2005;28(5):1113–7.
10. Smoak IW. Hypoglycemia and embryonic heart development. Front Biosci. 2002;7:d307–18.
11. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. Semin Perinatol. 2000;24(2):107–15.
12. Coustan DR, Biastre S, Daley JM, Homko CJ, Kjos S, Laptook AR. Medical management of pregnancy complicated by Diabetes. 5th ed. Coustan DR, editor. Alexandria, Virginia: American Diabetes Association; 2013.
13. Egan AM, Murphy HR, Dunne FP. The management of type 1 and type 2 diabetes in pregnancy. QJM. 2015;108 (12):923–7.
14. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? Diabetes Care. 2011;34(7):1660–8.
15. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. Diabetes. 1980;29(12):1023–35.
16. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care. 2008;31(5):1060–79.
17. American. Diabetes. Association. Glycemic Targets. Diabetes Care. 2016;39(Suppl. 1):S39–S46.
18. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 2007;30 Suppl 2:S251–60.
19. Hernandez TL. Glycemic targets in pregnancies affected by diabetes: Historical perspective and future directions. Curr Diab Rep. 2015;15:565.
20. Maresh MJ, Holmes VA, Patterson CC, Young IS, Pearson DW, Walker JD, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care. 2015;38(1):34–42.
21. Prutsky GJ, Domecq JP, Wang Z, Carranza Leon BG, Elraiyah T, Nabhan M, et al. Glucose targets in pregnant women with diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2013;98(11):4319–24.
22. Middleton P, Crowther CA, Simmonds L, Muller P. Different intensities of glycaemic control for pregnant women with pre-existing diabetes. Cochrane Database Syst Rev. 2010(9):CD008540.
23. Moy FM, Ray A, Buckley BS. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. Cochrane Database Syst Rev. 2014;4:CD009613.
24. Buhling KJ, Winkel T, Wolf C, Kurzidim B, Mahmoudi M, Wohlfarth K, et al. Optimal timing for postprandial glucose measurement in pregnant women with diabetes and a non-diabetic pregnant population evaluated by the Continuous Glucose Monitoring System (CGMS). J Perinat Med. 2005;33(2):125–31.
25. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, et al. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care. 2004;27(5):1200–1.
26. Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. Blood. 1982;59(6):1348–50.
27. Damm P, Mersebach H, Rastam J, Kaaja R, Hod M, McCance DR, et al. Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated HbA1c and spikes of high glucose values in the third trimester. J Matern Fetal Neonatal Med. 2014;27(2):149–54.
28. American. Diabetes. Association. Management of Diabetes in Pregnancy. Diabetes Care. 2016;39(Suppl. 1): S94-S8.
29. Voormolen DN, DeVries JH, Evers IM, Mol BW, Franx A. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. Obstet Gynecol Surv. 2013;68(11):753–63.
30. Polsky S, Giordano D, Voelmle MK, Garcetti R, Garg SK. Using technology to advance type 1 diabetes care among women during the reproductive years and in pregnancy. Postgrad Med. 2016.

31. Bailey TS, Grunberger G, Bode BW, Handelsman Y, Hirsch IB, Jovanovic L, et al. American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient glucose monitoring consensus statement. Endocr Pract. 2016;22(2):231–61.
32. Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER. Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes—observations from a randomized controlled trial. Diabet Med. 2013;30(11):1374–81.
33. American.Diabetes.Association. American Diabetes Association Guide to Nutrition Therapy for Diabetes. 2 ed. Franz MJ, Evert AB, editors. Alexandria, Virginia: American Diabetes Association 2012.
34. Roskjær AB, Andersen JR, Ronneby H, Damm P, Mathiesen ER. Dietary advices on carbohydrate intake for pregnant women with type 1 diabetes. J Matern Fetal Neonatal Med. 2015;28:229–33.
35. Wolfe LA, Heenan AP, Bonen A. Aerobic conditioning effects on substrate responses during graded cycling in pregnancy. Can J Physiol Pharmacol. 2003;81(7):696–703.
36. Melzer K, Schutz Y, Boulvain M, Kayser B. Physical activity and pregnancy: cardiovascular adaptations, recommendations and pregnancy outcomes. Sports Med. 2010;40(6):493–507.
37. A.C.O.G. committee opinion. Exercise during pregnancy and the postpartum period. Int J Gynaecol Obstet. 2002;77(1):79–81.
38. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A Lit Rev Diabetologia. 2012;55(3):542–51.
39. Kumareswaran K, Elleri D, Allen JM, Caldwell K, Westgate K, Brage S, et al. Physical activity energy expenditure and glucose control in pregnant women with type 1 diabetes: is 30 minutes of daily exercise enough? Diabetes Care. 2013;36(5):1095–101.
40. Duker PN, Dunbar SA, Kirkman MS. Medical Management of Type 1 Diabetes. 6th ed. Kaufman FR, editor. Alexandria, Virginia: American Diabetes Association; 2012.
41. Garcia-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia. 2010;53(3):446–51.
42. Lambert K, Holt IG. The use of insulin analogues in pregnancy. Diabetes Obes Metab. 2013;15:888–900.
43. Lenhard MJ, Kinsley BT. Insulin therapy for the treatment of type 1 diabetes during pregnancy. J Matern Fetal Neonatal Med. 2014;27(12):1270–5.
44. Varewijck AJ, Goudzwaard JA, Brugts MP, Lamberts SW, Hofland LJ, Janssen JA. Insulin glargine is more potent in activating the human IGF-I receptor than human insulin and insulin detemir. Growth Horm IGF Res. 2010;20 (6):427–31.
45. Dalfra MG, Soldato A, Moghetti P, Lombardi S, Vinci C, De Cata AP, et al. Diabetic pregnancy outcomes in mothers treated with basal insulin lispro protamine suspension or NPH insulin: a multicenter retrospective Italian study. J Matern Fetal Neonatal Med. 2016;29(7):1061–5.
46. de Jong J, Garne E, Wender-Ozegowska E, Morgan M, de Jong-van den Berg LT, Wang H. Insulin analogues in pregnancy and specific congenital anomalies: a literature review. Diabetes Metab Res Rev. 2015.
47. Humalog 200 Units/ml KwikPen, solution for injection in pre-filled pen. Summary of Product Characteristics Updated 18-Jan-2016 Basingstoke, Hampshire, UK: Eli Lilly and Company Limited; 2016.
48. Ciaraldi TP, Carter L, Seipke G, Mudaliar S, Henry RR. Effects of the long-acting insulin analog insulin glargine on cultured human skeletal muscle cells: comparisons to insulin and IGF-I. J Clin Endocrinol Metab. 2001;86 (12):5838–47.
49. Kurtzhals P, Schaffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes. 2000;49(6):999–1005.
50. Lepercq J, Lin J, Hall GC, Wang E, Dain MP, Riddle MC, et al. Meta-Analysis of Maternal and Neonatal Outcomes Associated with the Use of Insulin Glargine versus NPH Insulin during Pregnancy. Obstet Gynecol Int. 2012;2012:649070.
51. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brondsted L, Jovanovic L, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35(10):2012–7.
52. Hod M, Mathiesen ER, Jovanovic L, McCance DR, Ivanisevic M, Duran-Garcia S, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. J Matern Fetal Neonatal Med. 2014;27(1):7–13.
53. Gimenez M, Conget I, Nicolau J, Pericot A, Levy I. Outcome of pregnancy in women with type 1 diabetes intensively treated with continuous subcutaneous insulin infusion or conventional therapy. A case-control study. Acta Diabetol. 2007;44(1):34–7.
54. Volpe L, Pancani F, Aragona M, Lencioni C, Battini L, Ghio A, et al. Continuous subcutaneous insulin infusion and multiple dose insulin injections in Type 1 diabetic pregnant women: a case-control study. Gynecol Endocrinol. 2010;26(3):193–6.

55. Gonzalez-Romero S, Gonzalez-Molero I, Fernandez-Abellan M, Dominguez-Lopez ME, Ruiz-de-Adana S, Olveira G, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with type 1 diabetes. Diabetes Technol Ther. 2010;12(4):263–9.
56. Pozzilli P, Battelino T, Danne T, Hovorka R, Jarosz-Chobot P, Renard E. Continuous subcutaneous insulin infusion in diabetes: patient populations, safety, efficacy, and pharmacoeconomics. Diabetes Metab Res Rev. 2016;32:21–39.
57. Kekalainen P, Juuti M, Walle T, Laatikainen T. Continuous Subcutaneous Insulin Infusion During Pregnancy in Women with Complicated Type 1 Diabetes Is Associated with Better Glycemic Control but Not with Improvement in Pregnancy Outcomes. Diabetes Technol Ther. 2015.
58. Talaviya PA, Saboo BD, Joshi SR, Padhiyar JN, Chandarana HK, Shah SJ, et al. Pregnancy outcome and glycemic control in women with type 1 diabetes: a retrospective comparison between CSII and MDI treatment. Diabetes Metab Syndr. 2013;7(2):68–71.
59. Neff KJ, Forde R, Gavin C, Byrne MM, Firth RG, Daly S, et al. Pre-pregnancy care and pregnancy outcomes in type 1 diabetes mellitus: a comparison of continuous subcutaneous insulin infusion and multiple daily injection therapy. Ir J Med Sci. 2014;183(3):397–403.
60. Bernasko J. Insulin pump therapy for pregnancy: a primer. J Matern Fetal Neonatal Med. 2012;25(6):552–7.
61. Maso G, Piccoli M, Parolin S, Restaino S, Alberico S. Diabetes in pregnancy: timing and mode of delivery. Curr Diab Rep. 2014;14(7):506.
62. Hofmeyr GJ, Hannah M, Lawrie TA. Planned caesarean section for term breech delivery. Cochrane Database Syst Rev. 2015;7:CD000166.
63. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51(5):726–35.
64. Algert CS, McElduff A, Morris JM, Roberts CL. Perinatal risk factors for early onset of Type 1 diabetes in a 2000-2005 birth cohort. Diabet Med. 2009;26(12):1193–7.
65. Khashan AS, Kenny LC, Lundholm C, Kearney PM, Gong T, Almqvist C. Mode of obstetrical delivery and type 1 diabetes: a sibling design study. Pediatrics. 2014;134(3):e806–13.
66. Taylor R, Lee C, Kyne-Grzebalski D, Marshall SM, Davison JM. Clinical outcomes of pregnancy in women with type 1 diabetes. Obstet Gynecol. 2002;99(4):537–41.
67. Achong N, Duncan EL, McIntyre HD, Callaway L. Peripartum management of glycemia in women with type 1 diabetes. Diabetes Care. 2014;37(2):364–71.

Part III
Global Findings in Gestational Diabetes

Chapter 7
Maternal Diabetes in Pregnancy: Iran Perspectives

Lida Moghaddam-Banaem

Key Points

- Gestational diabetes is a rather common metabolic pregnancy disorder in Iran with an approximate prevalence of 3.5%.
- The prevalence of gestational diabetes varies greatly in different parts of Iran; namely from 0.7% in western regions to 18.6% in central parts.
- The recognized risk factors for gestational diabetes in Iran do not differ much from the established risk factors all over the world, i.e., increasing age and body mass index, and history of gestational diabetes.
- Iran has been implementing World Health Organization guidelines for gestational diabetes in safe motherhood programs for more than a decade.
- The Ministry of Health and Medical Education in Iran needs to announce at least yearly statistics about gestational diabetes.

Keywords Gestational diabetes mellitus · Iran · Prevalence · Risk factors · Screening

Abbreviations

GDM	Gestational diabetes mellitus
GCT	Glucose challenge test
OGTT	Oral glucose tolerance test
NDDG	National diabetes data group
BMI	Body mass index
WHO	World Health Organization
ACOG	American Congress of Obstetrics and Gynecology

Introduction

Maternal Diabetes in pregnancy or **Gestational Diabetes Mellitus (GDM)** is an important metabolic complication in pregnancy with a wide range of occurrence between 1 and 14% all over the world [1]. This metabolic disturbance which is due to carbohydrate intolerance is diagnosed or initiated first in

L. Moghaddam-Banaem (✉)
Department of Midwifery and Reproductive Health, Faculty of Medical Sciences, Tarbiat Modares University, Al-e-Ahmad Highway, Tehran, Iran
e-mail: moghaddamb@modares.ac.ir; lsmoghaddam3@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_7

pregnancy in a previously healthy mother with no clinical or laboratory evidence of diabetes or hyperglycemia. GDM may lead to unfavorable maternal and fetal outcomes such as macrosomia, birth trauma, and respiratory distress syndrome in newborns [2]; and induced labor, caesarean section in mothers [3]. Recent studies have indicated that the offspring of GDM mothers may be more vulnerable to adulthood obesity and type 2 diabetes [2]. On the other hand, the mother herself may be at greater risk for future type 2 diabetes, and also cardiovascular disorders. There is growing evidence suggesting that GDM may be an early marker of metabolic syndrome, because of the increasing incidence of metabolic syndrome in women with GDM history [4].

In Iran, there is a 4.9% estimated prevalence of GDM which varies greatly between different regions, from 0.7% in *Kermanshah* in west of Iran to 18.6% in *Karaj*-near Tehran [5]. There have been a great number of studies performed in Iran to investigate GDM risk factors, consequences, and overall incidence. In the present chapter, the prevalence and risk factors of GDM, and the current applied guidelines regarding GDM in Iran are discussed.

Gestational Diabetes Prevalence in Iran

The Ministry of Health and Medical Education in Iran has not presented the official statistics about GDM prevalence yet, but there have been many investigations about the prevalence of GDM in different parts of Iran over the years. In a rather extensive review published in 2009 [6], the results of 18 studies in different regions of Iran between 1992 and 2007 were reported and compared; the majority of the studies were performed in Tehran, but other provinces, i.e., *Mazandaran* (north), *Semnan, Yazd, Isfahan* (all in center), *Kermanshah* (west), *Lorestan* (south-west), *Ardabil* (north-west), *Kerman, Bushehr, Hormozghan* (all in south) were assessed too. The highest prevalence of GDM was reported in Hormozghan (8.9%) which detected GDM based on *Carpenter and Coustan* criteria. The lowest prevalence was 1.3% observed in Ardabil based on NDDG (National Diabetes Data Group) criteria. In other regions including Tehran, GDM prevalence varied from 3.5 to 7%.

In 2005 a study in *Bandar Abbas* (south of Iran) revealed an 8.9% prevalence of GDM by Carpenter & Coustan criteria [7]. In *Babol* (north of Iran) in a study in 2007 the prevalence of GDM was reported to be 4.7% [8]. In many studies there is a considerable difference in GDM prevalence between north and south of Iran, which may be quite probably due to lifestyle differences between the two regions. A study in Tehran in 2008 reported a 6.8% prevalence of GDM with a positive Glucose Challenge Test (GCT) among 38.1% of studied mothers [9]. In *Shahrood* (approximately in the central region of Iran), a study on 1310 pregnant women showed a 4.8% prevalence of GDM with *Carpenter & Coustan* criteria [10].

In a more recent systematic review in 2015 on 21 published articles, general GDM prevalence in Iran was reported to be 3.4%, while this rate in *Tehran* varied from 2.3 to 6.9%; the lowest prevalence was observed in a study in *Kermanshah* (0.7%) and the highest in *Karaj* (18.6%) [5]. Thus this wide difference should be noted by health policy makers, when developing preventive strategies for GDM.

GDM Risk Factors in Iran

There are some established risk factors for GDM, i.e., obesity or being overweight, familial history of diabetes, advanced age, etc. [11]. In different parts of Iran, there have been many studies performed to define the specific regional risk factors for GDM.

In the systematic review and meta-analysis published in 2015, the following risk factors were identified for GDM in Iranian context: *history of gestational diabetes, family history of diabetes, high*

body mass index (BMI), increasing number of live children and abortions, and history of macrosomia [1]. In another study in *Bandar Abbas* the risk factors identified for GDM were: *age, number of pregnancies, history of macrosomia, and BMI* [7]. In *Babol* the only risk factor identified for GDM was the *mother's age* [8]. A study in 2008 revealed these risk factors to be significant in pregnant women in Tehran: *age, pre-pregnancy BMI, diabetes' familial history, GDM history, and chronic hypertension* [9]. The *Shahrood* study found that the *age of mother older than 30 years, family history of diabetes, obesity, and history of macrosomia* were the significant risk factors for GDM [10].

There have been other GDM potential risk factors investigated in the Iranian context, such as a study in 2013 in Tehran which demonstrated that among nutritional intake and serum levels of iron and zinc in first half of pregnancy, the only significant factor was early pregnancy serum iron levels which had a direct effect on later occurrence of GDM [12]. In another study in Mashad (north-east of Iran) on several micronutrients, i.e., Ni, Al, Cr, Mg, Fe, Zn, Cu, Se, and risk of gestational diabetes, the only significant factor was serum iron level which had a surprisingly inverse relation with GDM [13]. In another study in Tehran, it was found that low urine calcium–creatinine ratio in early pregnancy is related to GDM [14].

As observed above, there are not many differences among GDM risk factors in Iranian mothers and the established risk factors all over the world; obesity and increasing age being the most common ones in the majority of the studies.

GDM Screening in Iran

The screening program for detecting gestational diabetes during pregnancy in Iran started in 1999 in the form of a pilot study in rural and urban health centers of multiple provinces. After several years of successful administration of this pilot screening and obtaining beneficial results in the general health of mothers and infants, this program was integrated in the comprehensive maternal healthcare services in Iran in 2006. For the past 10 years all pregnant women under coverage for safe motherhood programs in urban and rural health centers of Iran have been provided with the screening program for detection of GDM and if detected, with treatment and being managed properly during pregnancy to reduce the harmful effects of GDM on mother and infant.

GDM Screening Guidelines Used in Iran

When first implemented in the safe motherhood program, GDM screening was performed according to The American Congress of Obstetrics and Gynecology (ACOG) recommendation, as a two-step program; first all pregnant women with gestational age between 24 and 28 weeks were assessed by a Glucose Challenge Test (GCT) with ingestion of 50 g glucose solution in non-fasting condition, and if blood sugar after 1 h of glucose ingestion was higher than 140 mg/dL, then a 3-h oral Glucose Tolerance Test (OGTT) with 100 g glucose solution in fasting condition would be performed. The criteria used in Iran for GDM diagnosis is *Carpenter & Coustan* criteria which indicates that if two values of the four obtained blood sugar levels are higher than the recommended thresholds (95, 180, 155, and 140 mg/dL for fasting, 1, 2, and 3 h after glucose ingestion respectively) then the mother is diagnosed with GDM.

The NDDG (National Diabetes Data Group) criteria which has higher thresholds for GDM diagnosis (105, 190, 165, and 145 mg/dL for fasting; 1, 2, and 3 h after glucose ingestion respectively), is not commonly used in Iran, but some obstetricians or laboratories may apply it for some patients.

When ***World Health Organization (WHO)*** and ***International Association of Diabetes and Pregnancy Study Groups (IADPSG)*** announced the one-step screening program (75 g Glucose 2-h OGTT) for GDM diagnosis in 2013 [15], the Iranian Ministry of Health and Medical Education proclaimed it to be applied in all Iranian urban and rural health centers too.

The current guideline used for detecting GDM in pregnancy in Iran, which is derived from the above mentioned program is described below [16].

Current GDM Screening and Diagnosis Guideline in Iran

First Prenatal Visit

A fasting blood sugar (FBS) test is required for all pregnant mothers at their first prenatal visit (Table 7.1):

- $93 < FBS < 125$ mg/dL: The mother is considered to be prediabetic and is provided with appropriate exercise and nutritional programs.
- $FBS \geq 126$ mg/dL: The test should be repeated once more, and if the resulting FBS is still equal to or more than 126 mg/dL, the mother is considered to be diabetic and should be treated accordingly by an obstetrician.

Important point: An appropriate exercise and nutritional program from the beginning of pregnancy can prevent the occurrence of gestational diabetes.

GDM Screening

All pregnant women at 24–28 weeks of gestation should undergo a 2-h oral glucose tolerance test (OGTT) with 75 g glucose. If one or more of the results are abnormal, the mother is diagnosed with gestational diabetes and referred to an obstetrician for therapeutic and nutritional recommendations, and is followed up by the healthcare staff accordingly (Table 7.2).

Table 7.1 FBS interpretation at the first prenatal visit

FBS (mg/dL)	≤ 92	Normal
	93–125	Prediabetic
	≥ 126	Diabetic

Table 7.2 Blood sugar (BS) thresholds for the 2-h 75 g glucose OGTT

Fasting	≥ 92	Abnormal result
1 h after glucose ingestion (mg/dL)	≥ 180	
2 h after glucose ingestion (mg/dL)	≥ 153	

Table 7.3 Interpretation of the 2-h 75 g glucose OGTT post-partum

FBS (mg/dL)	≤ 99	Normal
	100–125	Prediabetic
	≥ 126	Diabetic
BS 2 h after glucose ingestion	<140	Normal
	140–199	Prediabetic
	≥ 200	Diabetic

Post-Partum Recommendations

All mothers with GDM should undergo 2-h 75 g glucose OGTT at 6–12 weeks post-partum to detect diabetes. The results' interpretation is demonstrated in Table 7.3.

- For diabetic women, diabetes treatment should be started.
- For prediabetic women, life style changes (improved exercise and nutritional habits) or Metformin use is recommended.
- For women with normal results, diabetes screening every 3 years is recommended.

Conclusion

The prevalence of gestational diabetes in Iran is rather lower than many countries in the world especially industrialized ones, but varies greatly in different parts of the country, thus needing more strategic planning to prevent new cases from developing in high prevalence regions and also confronting the consequences in current cases. The Ministry of Health and Medical Education in Iran needs to announce at least yearly statistics about gestational diabetes to enable better planning for combating this challenge.

References

1. Jafari-Shobeiri M, et al. Prevalence and risk factors of gestational diabetes in Iran: a systematic review and meta-analysis. Iran J Public Health. 2015;44(8):1036–44.
2. Yessoufou, A, Moutairou K. Maternal diabetes in pregnancy: early and long-term outcomes on the offspring and the concept of "metabolic memory". Exp Diab Res. 2011;2011:12.
3. Alavinia SM, et al. Gestational diabetes mellitus in Iran–experience from the national diabetes program. Int J Pharm Healthc Mark. 2012;6(2):156–66.
4. Xu Y, et al. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS ONE. 2014;9(1):e87863.
5. Sayehmiri F, et al. Prevalence of gestational diabetes mellitus in Iran: a systematic review and meta-analysis study. Iran J Obstet Gynecol Infertility. 2013;15(40):16–23.
6. Khoshnniat Nikoo M, Abbaszadeh Ahranjani S, Larijani B. A review on the prevalence of gestational diabetes mellitus (GDM) in different regions of Iran. J Diab Metab Disord. Available at: http://jdmd.tums.ac.ir/index.php/jdmd/article/view/239 2009;**7**:10.
7. Hadaegh F, et al. Prevalence of gestational diabetes mellitus in southern Iran (Bandar Abbas City). Endocr Pract. 2005;11(5):313–8.
8. Asnafi N, Taheri B. Incidence of gestational diabetes mellitus in Babol (north of Iran) (2002–03). J Gorgan Univ Med Sci. 2007;8(4):5.
9. Garshasbi A, et al. Prevalence and risk factors for gestational diabetes mellitus in Tehran. J Family Reprod Health. 2008;2(2):6.

10. Keshavarz M, et al. Gestational diabetes in Iran: incidence, risk factors and pregnancy outcomes. Diab Res Clin Pract. 2005;69(3):279–86.
11. Cypryk K, et al. Gestational diabetes mellitus-an analysis of risk factors. Endokrynol Pol. 2008;59(5):393–7.
12. Behboudi-Gandevani S, Safary K, Moghaddam-Banaem L. The relationship between maternal serum iron and zinc levels and their nutritional intakes in early pregnancy with gestational diabetes. Biol Trace Elem Res. 2013; 154(1):7–13.
13. Akhlaghi F, Bagheri SM, Rajabi O. A comparative study of relationship between micronutrients and gestational diabetes. ISRN Obstet Gynecol. 2012;2012:470419.
14. Safary K, Ahmed HM, Moghaddam-Banaem L. Maternal calcium status in first half of pregnancy and gestational diabetes mellitus. Int J Womens Health Wellness. 2016;2(1):5.
15. Organization WHO. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Geneva: World Health Organization; 2013.
16. Office of Maternal Health, B.o.F.H.a.P., Ministry of Health and Medical Education. National program for safe motherhood: integrated maternal health care. Tehran: Negah Electronic charter; 2013.

Chapter 8
25-Hydroxyvitamin D and Its Impact on Pregnancy Outcomes and Gestational Diabetes in China

Jing Zhou, Xiaopei Cao and Haipeng Xiao

Keywords 25-hydroxyvitamin D · Maternal · Fetal · Pregnancy · Outcome

Abbreviations

25(OH)D	25-hydroxyvitamin D
1,25(OH)2D	1,25-dihydroxyvitamin D
GDM	Gestational diabetes mellitus
SGA	Small for gestational age
LBW	Low birth weight
PE	Preeclampsia

Key Points

- Vitamin D deficiency among pregnant women is highly prevalent among all races and in all age groups worldwide, and its incidence has been rising in the past 10 years.
- Vitamin D deficiency is defined as serum 25(OH)D $\leq$ 50 nmol/L {less than or equal to 20 ng/ml}.
- Vitamin D deficiency during pregnancy has been associated with certain maternal, fetal, and neonatal complications.
- Population studies across different cities in China showed a prevalence of over 60% of vitamin D deficiency or insufficiency in pregnant women.
- Vitamin D deficiency may be associated with insulin resistance and is a risk factor for GDM.
- To date, no consensus exists regarding optimal vitamin D level in pregnancy.

J. Zhou (✉)
Department of Endocrinology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, 107 Yanjiangxi Road, Guangzhou, China
e-mail: zhjstudio@gmail.com

X. Cao · H. Xiao
Department of Endocrinology, First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan Road 2, Guangzhou, China
e-mail: caoxp@mail.sysu.edu.cn

H. Xiao
e-mail: xiaohp@mail.sysu.edu.cn

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_8

Introduction

Vitamin D deficiency has a high prevalence among all races and ethnicities and in all age groups worldwide [1]. Its incidence has been rising in the past 10 years. It is estimated that at least 1 billion people worldwide are inflicted by vitamin D deficiency or insufficiency [2]. Increasing evidence demonstrates that vitamin D deficiency during pregnancy is associated with the maternal, fetal, and neonatal complications, including death and malformations. Coupled with its high prevalence, it makes vitamin D deficiency a major health concern and burden for women of child-bearing age in developing countries. An estimated 9–10% of pregnant women (about 14 million) per year suffer from acute maternal complications worldwide [3, 4]. Several studies suggest that low 25(OH)D predicts increased risk of gestational diabetes mellitus (GDM), preeclampsia (PE), threatened preterm birth, cesarean section, and low birth weight (LBW), although other studies found no significant associations with these outcomes [5–7]. As a recent review of vitamin D and pregnancy outcomes concluded, the quality of evidence is still low [8]. To date, no consensus exists regarding optimal vitamin D level in pregnancy.

Definitions

The molecule of vitamin D (D3 or D2) is hydroxylated and converted to 25-hydroxyvitamin D [25 (OH)D], which in turn undergoes a second hydroxylation primarily in the kidney (but in many other tissues as well). This results in the formation of 1,25-dihydroxyvitamin D [calcitriol, 1,25(OH)2D], the biologically active metabolite of vitamin D. 25(OH)D is the major storage form of vitamin D in human. As it can be measured in blood, it has become the most accepted indicator of vitamin D nutritional status [9]. Based on the 25(OH)D level, vitamin D deficiency is defined as serum 25(OH) D $\leq$ 50 nmol/L {less than or equal to 20 ng/ml}, and was further categorised into severe deficiency ($\leq$ 25 nmol/L) and mild deficiency (25–50 nmol/L). Serum 25(OH)D between 50 and 75 nmol/L {21–29 ng/ml} was defined as vitamin D insufficiency, and serum 25(OH)D above 75 nmol/L {greater than or equal to 30 ng/ml} was defined as vitamin D sufficiency [2] (Table 8.1).

Table 8.1 Definition of vitamin D status [2]

Vitamin D status	Range	
	(nmol/L)	(ng/ml)
Severe deficiency	$\leq$ 25	$\leq$ 10
Mild deficiency	25–50	10–20
Insufficiency	50–75	21–29
Sufficiency	$\geq$ 75	$\geq$ 30
Toxicity	>250	>100

High Prevalence of Vitamin D Deficiency Among Pregnant Women

During pregnancy, there is significant increase in maternal serum 1,25(OH)2D metabolisms on account of the extra calcium required for fetal bone mineralization. However, vitamin D deficiency among pregnant women has been reported in all race, ethnicities, and age groups worldwide [10–17] (Table 8.2). From the data reported, it seems that the prevalence of vitamin D deficiency differs according to skin complexion. The highest rate has been found in individuals with dark skin (especially African American), intermediate in Asians with yellow skin and the lowest rate found in Caucasians with white skin [10, 14–17]. The prevalence is higher in northern compared to southern regions of the Northern hemisphere [12, 14, 16, 17]. Vitamin D deficiency is also found among pregnant and lactating women who take a prenatal vitamin D and a calcium supplement [18–20]. Longitudinal studies of vitamin D status during pregnancy have shown that vitamin D levels increase with gestational duration, such that the lowest levels being found in the first trimester and the highest levels in late phases of pregnancy [10, 14].

The prevalence of vitamin D deficiency among Chinese pregnant women is consistent with findings in other countries. In China, mean levels of 25(OH)D among pregnant women were 27.03 ± 7.92, 17.57 ± 11.44, 14.38 ± 7.88 ng/ml with 18.9, 69, 57.1% of vitamin D deficiency in Guangzhou [21], Shanghai [22], and Chengdu [23], respectively. In urban Beijing [24] and Wuxi [25], where the mean serum 25(OH)D concentration in pregnant women was 28.64 and 34.0 nmol/L, respectively, severe vitamin D deficiency was detected in 54.5 and 40.7% pregnant women, respectively. Data from Shenyang, a city located in northern China, has reported a 37.2% vitamin D deficiency among pregnant women [26] (Table 8.3, location in Fig. 8.1).

Overall, the reported average rate of vitamin D deficiency or insufficiency among pregnant people in China exceeds 60% [12, 21–27].

The major two sources of vitamin D are exposure of the skin to solar ultraviolet B radiation and dietary intake. Cutaneous synthesis of vitamin D is under considerable influence of latitude, season,

Table 8.2 Vitamin D deficiency during pregnancy in different countries

Location	Sample size	Mean level of 25(OH)D (nmol/L)	Percentage of vitamin D deficiency (%)
S. Korean [10]	222	31.50 ± 1.75	77.3
Belgian [11]	1311	53.0(95% CI 51.3–55.5)	44.6
China [12]	1985	38.8(95% CI 29.8–50.0)	74.5
Saudi Arabia [13]	160	49.9(IQR = 28.0)	50
Swedish [14]	184	55.2 ± 17.5	35
Africa [15]	87	17.05 ± 12.85	97
Netherland [16]	7256	NA	26
Spain [17]	2036	75.5(95% CI 56.8–94.0)	18

Table 8.3 Vitamin D deficiency during pregnancy in cities in China

Location	Latitude	Mean level of 25(OH)D (nmol/L)	Percentage of vitamin D deficiency (%)
Guangzhou [21	23ºN	67.57	18.9
Shanghai [22]	31ºN	43.92	69
Chendu [23]	37.7ºN	48.5	57.1
Beijing [24]	39.9ºN	28.64	54.5
Wuxi [25]	31.5ºN	34.0	40.7
Shenyang [26]	41.8ºN	NA	37.2
Guiyang [27]	26ºN	36.72	83.6

Fig. 8.1 Locations of cities that had data of vitamin D deficiency in China

and time of day. The level of vitamin D can be influenced by multiple ethnic, geographical, seasonal, dietary, and physiological/pathological factors.

Several reasons are proposed to explain the high prevalence of vitamin D deficiency among Chinese pregnant women: (1) Low exposure to sunshine. Women, especially pregnant women, are more likely to avoid sun exposure. This may be due to recognition of ultraviolet as a potential stimulator of skin cancer, and/or due to pregnant women having a tendency to stop working and staying at home. Additionally, urbanization was shown to result in less frequent outdoor activity of individuals. (2) Dietary calcium intake is deficient. It has been reported that the annual consumption of milk per capita of China is much lower than its counterpart figures across the world [28]. (3) Vitamin D deficiency is possibly more common in yellow-skin people than that in Whites as the skin absorbs UV B radiation by melanin [29]. (4) Increased rate of pregnancy at a more advanced age. Social changes and professional advancement have made women to increasingly prefer to get married and become pregnant later in life. Aging reduces vitamin D synthesis, so advanced pregnancy age may contribute to higher vitamin D deficiency rate. (5) Overweight and obesity among young Chinese population are much more prevalent than a few decades ago. Body fat can sequestrate vitamin D resulting in a reduction of available circulating vitamin D.

Although all these factors may play a role, the exact causes contributing to the high prevalence of vitamin D deficiency in pregnant Chinese women remain to be elucidated in future studies.

The observations pointing to variations between different cities may be due to several reasons. The most important one is the degree of sunlight exposure. At higher latitude, less UV B radiation reaches the earth and less vitamin D can be synthesized. Several studies have shown that maternal vitamin D

level markedly increased from the beginning of summer, peaked in July, declined through autumn and remained low in winter and spring in China [21, 25–27]. Seasonal variation in 25(OH)D status was also observed in American [14], Australian [30], and Indian [31] pregnant women. Similar observation was reported in a Guangzhou study [26] which showed a strong positive correlation between serum 25(OH)D level and the average temperature of the month.

Vitamin D Deficiency and Pregnancy Outcomes

Several studies have demonstrated that vitamin D deficiency or insufficiency in pregnant women is associated with increased risk of adverse pregnancy and neonatal outcomes as well as mother and child lifelong health. Such pregnancy and neonatal events include PE, recurrent miscarriage, premature rupture of membranes (PROM), preterm delivery, cesarean section, intrauterine growth restriction, LBW infants, and GDM [31].

High prevalence and increased severity of maternal vitamin D deficiency has been associated with increased risk of preterm delivery. A report from Shenyang, a northeast city in China, has described a 63.04% rate of vitamin D deficiency among mothers that delivered very preterm babies, which was almost twice the percentage in mothers of normal deliveries (36.61%) [26]. Maternal vitamin D deficiency during pregnancy also increases the risks of LBW infants and small for gestational age (SGA) infants. In a population-based birth cohort study [32], there was a positive correlation between maternal serum 25-hydroxyvitamin D level and offspring birth weight ($r = 0.477$, $P < 0.001$). Further analysis showed that among mothers with vitamin D deficiency, 4.98% delivered neonates who were LBW infants compared to a rate of 1.32% among the subjects with vitamin D insufficiency. Moreover, 16.01% of neonates of mothers with vitamin D deficiency were SGA infants, compared with 5.59% of neonates of subjects with vitamin D insufficiency. The association between maternal vitamin D status and the risks of SGA and LBW infants existed regardless of the different gestational stages.

In contrast, a population-based birth cohort study in Guangzhou [21], a southern city in China, has reported no significant relationships between maternal vitamin D status and most of the adverse maternal outcomes (PROM, polyhydramnios, oligohydramnios, PE, cesarean section) except for GDM. Mothers with vitamin D deficiency at 16–20 gestational week had higher prevalence of gestational diabetes (adjusted OR 1.017; 95% CI 1.002–1.033) and preterm delivery (adjusted OR 1.038; 95% CI 1.018–1.059) than those with sufficient vitamin D.

Although the mechanisms underlying the above observations have not been elucidated, vitamin D has pleiotropic effects, and is involved in bone metabolism, human chorionic gonadotropin expression, and placental sex steroid production. It may therefore have an important role in fetal growth, development, and newborn outcomes. Vitamin D status of a newborn is mostly dependent on that of the mother. Thus, low maternal vitamin D level may lead to neonatal vitamin D deficiency with subsequent adverse effects on the fetus, including small for gestational size, neonatal hypocalcaemia and seizures, impaired growth and skeletal problems, neuronal differentiation, endocrine functions, fetal brain growth, neonatal rickets and tetany, infant rickets, and low bone mineral density (BMD).

In addition, there are growing concerns pertaining to the long-term effects of maternal vitamin D deficiency on the child's later life health. Studies suggested that insufficient fetal vitamin D may be associated with increased risk of childhood autism [33], respiratory infections [34], food sensitivities, atopic dermatitis, eczema, and asthma [35]. A recent study showed that vitamin D sufficiency in early pregnancy may be associated with risk of metabolic syndrome in the offspring [36].

More well-designed prospective randomized controlled clinical trials of vitamin D supplementation during pregnancy are needed to evaluate the potential role of vitamin D to prevent lifelong adverse outcomes.

Vitamin D Deficiency and Gestational Diabetes

Evidence suggests that vitamin D may play a role in maintaining normal glucose homeostasis. In experimental studies, vitamin D was implicated immediating both direct (through activation of vitamin D receptor) and indirect (via regulation of calcium homeostasis) effects on various mechanisms related to the pathophysiology of diabetes, including pancreatic beta-cell dysfunction, impaired insulin action and sensitivity, and systemic inflammation [37]. Some studies reported that GDM women have lower 25(OH)D levels in comparison with pregnant women with normal glucose level [38]. A number of reports have confirmed that those with vitamin D deficiency have an increased risk of developing GDM [39]. Vitamin D sufficiency in pregnancy appears to be related to lower fasting and 2 h postprandial glucose level, lower glycosylated hemoglobin, improved insulin levels, and insulin sensitivity [40]. However, the role of vitamin D in glucose homeostasis during pregnancy and the development of GDM remain inconclusive.

Evidence of prevalence of GDM in relation to different levels of maternal vitamin D in China is limited. One study in Guangzhou, China did not show an association between prevalence of GDM and different levels of maternal vitamin D [21]. However, another study from Beijing, China showed that subjects with 25(OH)D levels <25 nmol/L had a 1.8-fold higher risk of GDM compared with subjects with higher vitamin D levels [40]. In the GDM group, serum 25(OH)D level was independently associated with HbA1c and insulin resistance after adjusting for confounding factors. These findings indicate that low 25OHD status may be associated with insulin resistance and act as a risk factor for GDM.

Two recent meta-analyses have shown that pregnant women with GDM tended to have significantly lower circulating vitamin D levels [41, 42]. However, after adjusting for potential confounders (age, body mass index, season, etc.), there were no difference between women with and without GDM. Thus, good-quality randomized prospective trials are required to determine whether vitamin D deficiency increases the risk of GDM in pregnant women.

Vitamin D Supplementation for Pregnant Women, Beneficial or Not?

To date, supplementation of vitamin D is not a part of routine preterm care programs in China.

Several studies have suggested that 25(OH)D concentration should be maintained above 20 ng/ml to prevent children and adults from rickets and osteomalacia [2, 43]. Furthermore, the concentration should be above 30 ng/ml to maximize 25(OH)D effect on calcium, bone, and muscle metabolism. This has benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases [2].

The estimated average requirement of vitamin D during pregnancy needs to be doubled, as the increase in the requirement of calcium ranges from 33 to 50% [44]. The recommend dietary allowances (RDA) of the institute of medicine (IOM) recommended 600 IU as the dietary reference intake for vitamin D during pregnancy.

However, several recent studies have indicated that even this RDA may not be adequate. [45] New guidelines suggest that pregnant and lactating women require at least 600 IU/d of vitamin D and recognize that at least 1500–2000 IU/d of vitamin D may be needed to maintain a blood level of 25 (OH)D above 30 ng/ml [2]. As vitamin D deficiency is common among pregnant women and is implicated in adverse pregnant outcomes, pregnant women are strongly encouraged to increase sunlight exposure and dietary calcium intake.

Vitamin D supplementation during pregnancy increases 25(OH)D levels significantly. There is some evidence that vitamin D supplementation could reduce the risk of PE, LBW, preterm birth and

may also increase newborn's length [46]. However, the benefits on pregnancy outcomes are still controversial. Meta-analysis of 13 RCTs showed no influences of vitamin D supplementation on the incidence of PE, GDM, SGA, LBW, preterm birth, and cesarean section [47]. A recently published multicenter, double-blind, randomized placebo-controlled trial, The Maternal Vitamin D Osteoporosis Study (MAVIDOS) [48], has found no increase in offspring whole-body bone mass by administering 1000 IU/day vitamin D supplementation during pregnancy. Similar negative conclusion was reached in the study of prenatal supplementation with vitamin D on offspring asthma or recurrent wheezing [49]. Taken together, the evidence on whether vitamin D supplementation should be given as a routine antenatal care to all women to improve maternal and infant outcomes remains debatable. Further high-quality randomized trials are required to evaluate the safety and effectiveness of vitamin D supplementation in pregnancy.

Conclusions

Vitamin D deficiency has a high prevalence in all races and ethnicities and in all age groups worldwide, and its incidence has been rising in the last decade. Pregnant and lactating women who take a prenatal vitamin and a calcium supplement with vitamin D still remain at high risk for vitamin D deficiency. This is also the case in China, whereby more than 60% prevalence of vitamin D deficiency or insufficiency was found among pregnant women across different cities.

Vitamin D level is influenced by the season of the year and by the geographical latitude. Variations between cities may be due, at least partly, to different degrees of sunshine exposure. The higher the latitude, the less UV B radiation reaches the earth and the less vitamin D that can be synthesized. Maternal vitamin D level markedly increases from the beginning of summer, peaks in July, and thereafter declines through autumn and remains low in winter and spring in China.

Vitamin D deficiency in pregnant women may be a cause for concern for pregnancy outcomes. Nonetheless, the data on the relationship between maternal vitamin D deficiency and pregnancy outcomes is often conflicting. High prevalence of maternal vitamin D deficiency may be associated with preterm and LBW/SGA infants, but probably not with other maternal outcomes including premature rupture of membranes break, polyhydramnios, oligohydramnios, preeclampsia, and cesarean section.

There is still scant evidence on the prevalence of gestational diabetes with respect to different levels of maternal vitamin D in China. The limited data on this possible association are conflicting, thereby mandating larger and preferably prospective studies.

To date, no consensus exists regarding the optimal vitamin D level in pregnancy. The estimated average requirement of vitamin D and calcium during pregnancy is higher than that required in non-pregnant individuals. On the basis of the high prevalence of maternal vitamin D deficiency, it seems appropriate to recommend that pregnant women in China should routinely be supplemented with vitamin D. However, further high-quality randomized controlled trials are pertinent in order to evaluate the safety and effectiveness of vitamin D supplementation in pregnancy.

References

1. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third national health and nutrition examination survey, 1988–1994. Am J Clin Nutr. 2002;76(1):187–92.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.

3. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards millennium development goal 5. Lancet. 2010;375(9726):1609–23.
4. Filippi V, Ronsmans C, Campbell OM, et al. Maternal health in poor countries: the broader context and a call for action. Lancet. 2006;368(9546):1535–41.
5. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. J Clin Endocrinol Metab. 2009;94(3):940–5.
6. Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM. Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. J Clin Endocrinol Metab. 2013;98(1):398–404.
7. Charatcharoenwitthaya N, Nanthakomon T, Somprasit C, et al. Maternal vitamin D status, its associated factors and the course of pregnancy in Thai women. Clin Endocrinol (Oxf). 2013;78(1):126–33.
8. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol. 2012;26(Suppl 1):75–90.
9. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84(1):18–28.
10. Choi R, Kim S, Yoo H, et al. High prevalence of vitamin D deficiency in pregnant Korean women: the first trimester and the winter season as risk factors for vitamin D deficiency. Nutrients. 2015;7(5):3427–48.
11. Vandevijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R. High prevalence of vitamin D deficiency in pregnant women: a national cross-sectional survey. PLoS ONE. 2012;7(8):e43868.
12. Yun C, Chen J, He Y, et al. Vitamin D deficiency prevalence and risk factors among pregnant Chinese women. Public Health Nutr. 2015;1–9.
13. Al-Faris NA. High prevalence of vitamin D deficiency among pregnant Saudi women. Nutrients. 2016;8(2).
14. Lundqvist A, Sandstrom H, Stenlund H, Johansson I, Hultdin J. Vitamin D status during pregnancy: A longitudinal study in Swedish women from early pregnancy to seven months postpartum. PLoS ONE. 2016;11(3):e150385.
15. Ayadi ID, Nouaili EB, Talbi E, et al. Prevalence of vitamin D deficiency in mothers and their newborns in a Tunisian population. Int J Gynaecol Obstet. 2016.
16. Vinkhuyzen AA, Eyles DW, Burne TH, et al. Prevalence and predictors of vitamin D deficiency based on maternal mid-gestation and neonatal cord bloods: the generation R study. J Steroid Biochem Mol Biol. 2015.
17. Rodriguez A, Santa ML, Jimenez AM, et al. Vitamin D status in pregnancy and determinants in a Southern European Cohort study. Paediatr Perinat Epidemiol. 2016;30(3):217–28.
18. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr. 2007;137(2):447–52.
19. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. Clin Pediatr (Phila). 2007;46(1):42–4.
20. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004;80(6 Suppl):1752S–8S.
21. Zhou J, Su L, Liu M, et al. Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: a prospective observational study in southern China. Eur J Clin Nutr. 2014;68(8):925–930.
22. Tao M, Shao H, Gu J, Zhen Z. Vitamin D status of pregnant women in Shanghai. China. J Matern Fetal Neonatal Med. 2012;25(3):237–9.
23. Wang J, Yang F, Mao M, Liu DH, Yang HM, Yang SF. High prevalence of vitamin D and calcium deficiency among pregnant women and their newborns in Chengdu, China. World J Pediatr. 2010;6(3):265–7.
24. Song SJ, Si S, Liu J, et al. Vitamin D status in Chinese pregnant women and their newborns in Beijing and their relationships to birth size. Public Health Nutr. 2013;16(4):687–92.
25. Xiao JP, Zang J, Pei JJ, Xu F, Zhu Y, Liao XP. Low maternal vitamin D status during the second trimester of pregnancy: a cross-sectional study in Wuxi, China. PLoS ONE. 2015;10(2):e117748.
26. Zhu T, Liu TJ, Ge X, Kong J, Zhang LJ, Zhao Q. High prevalence of maternal vitamin D deficiency in preterm births in northeast China, Shenyang. Int J Clin Exp Pathol. 2015;8(2):1459–65.
27. Xiang F, Jiang J, Li H, et al. High prevalence of vitamin D insufficiency in pregnant women working indoors and residing in Guiyang. China. J Endocrinol Invest. 2013;36(7):503–7.
28. Wat WZ, Leung JY, Tam S, Kung AW. Prevalence and impact of vitamin D insufficiency in southern Chinese adults. Ann Nutr Metab. 2007;51(1):59–64.
29. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet. 1982;1(8263):74–6.
30. Bowyer L, Catling-Paull C, Diamond T, Homer C, Davis G, Craig ME. Vitamin D, PTH and calcium levels in pregnant women and their neonates. Clin Endocrinol (Oxf). 2009;70(3):372–7.
31. Marwaha RK, Tandon N, Chopra S, et al. Vitamin D status in pregnant Indian women across trimesters and different seasons and its correlation with neonatal serum 25-hydroxyvitamin D levels. Br J Nutr. 2011;106 (9):1383–9.

32. Chen YH, Fu L, Hao JH, et al. Maternal vitamin D deficiency during pregnancy elevates the risks of small for gestational age and low birth weight infants in Chinese population. J Clin Endocrinol Metab. 2015;100(5):1912–9.
33. Fernell E, Bejerot S, Westerlund J, et al. Autism spectrum disorder and low vitamin D at birth: a sibling control study. Mol Autism. 2015;6:3.
34. Magnus MC, Stene LC, Haberg SE, et al. Prospective study of maternal mid-pregnancy 25-hydroxyvitamin D level and early childhood respiratory disorders. Paediatr Perinat Epidemiol. 2013;27(6):532–41.
35. Chiu CY, Huang SY, Peng YC, et al. Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood. Pediatr Allergy Immunol. 2015;26(4):337–43.
36. Munger KL, Aivo J, Hongell K, Soilu-Hanninen M, Surcel HM, Ascherio A. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the finnish maternity cohort. JAMA Neurol. 2016.
37. Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes Metab Res Rev. 2008;24(1):27–32.
38. Cho GJ, Hong SC, Oh MJ, Kim HJ. Vitamin D deficiency in gestational diabetes mellitus and the role of the placenta. Am J Obstet Gynecol. 2013;209(6):560–1.
39. Brannon PM. Vitamin D and adverse pregnancy outcomes: beyond bone health and growth. Proc Nutr Soc. 2012;71(2):205–12.
40. Wang O, Nie M, Hu YY, et al. Association between vitamin D insufficiency and the risk for gestational diabetes mellitus in pregnant Chinese women. Biomed Environ Sci. 2012;25(4):399–406.
41. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169.
42. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med. 2012;23(5):465–9.
43. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001–2006. NCHS Data Brief. 2011;59:1–8.
44. Yang HX. Diagnostic criteria for gestational diabetes mellitus (WS 331–2011). Chin Med J (Engl). 2012;125 (7):1212–3.
45. Afzal S, Bojesen SE, Nordestgaard BG. Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and metaanalysis. Clin Chem. 2013;59(2):381–91.
46. De-Regil LM, Palacios C, Lombardo LK, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2016;1:D8873.
47. Palacios C, De-Regil LM, Lombardo LK, Pena-Rosas JP. Vitamin D supplementation during pregnancy: updated meta-analysis on maternal outcomes. J Steroid Biochem Mol Biol. 2016.
48. Cooper C, Harvey NC, Bishop NJ, et al. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diab Endocrinol. 2016.
49. Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: The VDAART randomized clinical trial. JAMA. 2016;315(4):362–70.

Chapter 9
Diagnosis of Gestational Diabetes Mellitus: Italian Perspectives on Risk Factor-Based Screening

Francesco Corrado and Basilio Pintaudi

Key Points

- The current prevalence of gestational diabetes mellitus (GDM) according to the risk factor-based screening proposed by the Italian National Institute of Health is 11%.
- Limits of the established risk factors are acknowledged, being not all capable of correctly predicting the onset of GDM. Particularly, the risk factor of age over 35 years was not associated with GDM diagnosis.
- The utility of an alternative screening approach, based on risk stratification derived from the application of tree-growing regression techniques is proposed.
- The sensitivity of the procedure is 89% and specificity is 40%. It is not able to diagnose all the GDM cases but it is able to identify the majority of them and therefore has the advantage of saving economic resources.
- Results of a recent national Italian survey on the degree of healthcare professionals acceptance of the Italian guideline documented that almost one in five centers preferred a universal screening procedure, the others executing a selective risk factors-based screening as recommended by Italian guideline.
- The survey highlights some criticisms of current practices, related to (a) the selection of the appropriate method of risk factor-based screening and (b) to the right time for performing the diagnostic oral glucose-tolerance test in women at high risk of GDM.
- Stakeholders should consider all known risk factors for GDM if a selective screening approach is adopted.
- Scientific evaluation of risk models based on epidemiological data and population-based cohorts provide the foundation of future advancements in addressing the dilemma of finding optimal screening procedure for GDM.

Keywords Gestational diabetes · Screening · Diagnosis · Risk factor · Italian population · National institute of health guidelines

F. Corrado (✉)
Department of Obstetrics and Gynecology, A.O.U. Policlinico "G. Martino",
Policlinico Universitario, University of Messina, Via Consolare Valeria, 1, Messina, Italy
e-mail: fcorrado@unime.it

B. Pintaudi
Diabetic Unit, Niguarda Cà Granda, A.O. Ca' Granda Niguarda,
Piazza Ospedale Maggiore 3, Milano, Italy
e-mail: basiliopinta@yahoo.it; basilio.pintaudi@ospedaleniguarda.it

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_9

Abbreviations

GDM	Gestational diabetes mellitus
NICU	Neonatal intensive care unit
GCT	Glucose challenge test
NDDG	National Diabetes Data Group
ADA	American Diabetes Association
HAPO	Hyperglycemia and adverse pregnancy outcomes
IADPSG	International Association Of Diabetes In Pregnancy Study Group
RECPAM	RECursive Partitioning and AMalgamation

Introduction

Gestational diabetes mellitus (GDM) is defined as any carbohydrate intolerance with onset or fist recognition during pregnancy [1].

GDM occurs in about 11% of the Italian population [2, 3]. It is associated to an increased rate of maternal and fetal complications compared with normal pregnancy [4, 5]. Maternal complications, that occur with an increased frequency in mothers with GDM include: preterm delivery, polyhydramnios, macrosomia, shoulder dystocia, stillbirth and operative delivery. Fetal complications associated at an increased risk with GDM include: neonatal hypoglycemia, jaundice, polycythemia, hypocalcemia and increased frequency of neonatal intensive care unit (NICU) admission [4, 5].

In the majority of cases the glucose impairment determining GDM returns to normal at the end of the pregnancy. However, it may cause an impaired glucose tolerance later in life in the mother [6, 7] and contribute to features of metabolic syndrome [8] such as hypertension, dyslipidemia and microalbuminuria, which are linked to cardiovascular disease. Children of mothers with GDM have higher risks of childhood obesity and diabetes mellitus onset compared with those of mothers without GDM [9].

Fortunately, two important randomized controlled trials documenting the effect of appropriate GDM treatment in improving perinatal outcome have been published [10, 11].

The first study was performed by Crowther and the Australian Carbohydrate Intolerance Study in Pregnant Women Trial Group [10]. They randomly assigned 1000 women with GDM between 24 and 34 weeks gestation to receive dietary advice, blood glucose monitoring, and insulin therapy as needed (the intervention group) or standard obstetric care. The prevalence of serious complications such as death, shoulder dystocia, fractures, or nerve palsy was significantly reduced in the intervention group compared to the control group (1% vs. 4% $p = 0.01$) even after adjustment for confounding factors such as maternal age, race, and parity. Infants born to women in the intervention group also had a significantly reduced mean birth weight compared to the routine care group ($p = 0.001$) and a significantly lower percentage of large for gestational age and macrosomia infants was reported ($p = 0.001$).

The second study made by Landon et al. [11] involved a population of pregnant women with a mild carbohydrate intolerance who were positive (glycemia $\geq$135 mg/dl) to the 50 g 1 h glucose challenge test (GCT) but were not diagnosed as GDM in a subsequent oral glucose tolerance test (OGTT).

Of the 958 eligible patients 485 were randomly assigned to receive usual prenatal care (control group) and 473 to receive dietary intervention, self-monitoring of blood glucose, and insulin therapy, if necessary (treatment group). In this case no significant difference was reported for the primary outcomes (hypoglycemia, hyperbilirubinemia, elevated cord blood C-peptide, stillbirth, and birth

trauma) but a significant reduction in mean birth weight, rate of macrosomia and large for gestational age infants ($p = 0.001$) was reported in the intervention group.

However, in the light of the evidence from these two studies linking GDM to a set of fetal and maternal adverse outcomes, "the most important step in the management of gestational diabetes is its diagnosis. Once this has been achieved almost every type of management protocol has been associated with a reduction in the perinatal mortality rate" [12].

The first who provided a recognized method for the diagnosis of GDM was O'Sullivan in 1964 [13]. He observed the results of the 100 gr–3 h oral glucose tolerance test of 752 unselected consecutive pregnant women and decided to considered abnormal any glucose value that exceeds the upper limit of two standard deviations above the mean. According to these criteria an oral glucose tolerance test should be considered pathological when two or more glucose values are greater or equal 90, 165, 145, and 125 mg/dl for fasting, 1 h, 2 h, and 3 h after load, respectively. In the population of women identified as GDM according to these criteria an increased perinatal morbidity rate together with an increased prevalence of abnormal glucose tolerance later in life was reported (Table 9.1).

Unfortunately, in the O'Sullivan study the glucose values were measured using the Somogy-Nelson methods on whole blood. When the new and more accurate methodologies of enzymatic (glucose oxidase or hexokinase) assay on plasma were introduced as the standard practice in laboratories, we needed new cutoff values for GDM diagnosis. Consequently, several reinterpretations of the glucose values of the O'Sullivan study according to the new laboratory requirements were proposed. The most popular among them were the National Diabetes Data Group (NDDG) in 1979 [14] and the Carpenter and Coustan criteria in 1982 [15]. The last criteria was later accepted and included (Table 9.1) in the American Diabetes Association (ADA) guidelines published in 2000 [16]. At the same time the World Health Organization included the diagnostic criteria for the detection of diabetes in non-pregnant women also for the diagnosis of GDM [17].

Once the problem of diagnostic criteria was settled, another interesting question was ready behind the door: which patients should undergo the diagnostic oral glucose-tolerance test?

Great expectation was determined by the publication of the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in the 2008 [18]. Starting from the lack of international consensus regarding the diagnostic criteria for gestational diabetes, this study had been designed to determine the level of glucose intolerance in pregnancy associated with an impaired perinatal outcome. According to the results of the HAPO study, the International Association of the Diabetes and Pregnancy Study Group (IADPSG) panel proposed, in 2010, new criteria to diagnose GDM [19] trying to obtain a worldwide consensus on this new strategy. They proposed at first to consider a fasting glycemia $\geq$126 mg/dl, or a random glycemia $\geq$200 mg/dl, or a glycated hemoglobin $\geq$6.5% within the first trimester of pregnancy to exclude cases of preexisting diabetes. Moreover they proposed to consider a fasting glycemia $\geq$92 mg/dl but less than 126 mg/dl as diagnostic for GDM. Every pregnant women not already diagnosed, between 24 and 28 weeks, should undergo to a diagnostic 75 gr 2 h oral glucose tolerance test. To diagnose GDM glucose values should be equaling or exceeding 92, 180 and 153 mg/dl for fasting, 1 and 2 h post-load respectively. In this case only one value is enough for GDM diagnosis. These cutoff levels represent the glucose values over which

Table 9.1 Evolution of diagnostic criteria for gestational diabetes

	O'Sullivan* 1973	NDDG* 1979	Carpenter and Coustan* 1982	ADA* 2000
Fasting (mg/dl)	90	105	95	95
1-h after load	165	190	180	180
2-h after load	145	165	155	155
3-h after load	125	145	140	140

NDDG National Diabetes Data Group; *ADA* American Diabetes Association

*2 or more elevated values to have a diagnosis of gestational diabetes

women had a 75% higher risk (OR = 1.75) of having one of the adverse outcome considered in the study (birth weight ≥90th percentile, cord C-peptide ≥90th percentile, and percent body fat ≥90th percentile). Moreover the IADPSG panel proposed to extend the OGTT to all pregnant women without considering risk factors, although it was well known that some clinical or laboratory factors represent an indicator of an abnormal glucose tolerance in pregnancy, and have enough sensitivity to diagnose the majority of the affected pregnant women.

Unfortunately these guidelines did not reach the hoped worldwide consensus. At first the ADA did not accept the fasting value ≥92 and ≤126 mg/dl as diagnostic for GDM [20], later the American National Institutes of Health Consensus Conference did not recommend adoption of the IADPSG recommendation [21], and finally the American College of Obstetrics and Gynecologists continues to recommend the two-step diagnostic approach to screening using a cutoff for an abnormal 1-h screen of 135–140 mg/dl and two abnormal values on the 100 g–3 h oral glucose tolerance test, evaluated with NDDG or Carpenter and Coustan criteria [22].

Gestational Diabetes Diagnosis in Italy

In Italy since 2010 the reported GDM prevalence ranged between 3 and 7% [23, 24]. The most part of the clinical centers used for GDM diagnosis a two-steps method. A glucose challenge test with 50 grams glucose load and fasting and one hour post-load evaluation has been performed between 24 and 28 weeks of gestation. The population to test with this procedure varied according to single-center approach. Some centers followed a risk factor-based selective screening according to ADA [25]; others proposed the procedure to all pregnant women. A diagnostic oral glucose tolerance test with 100 grams glucose load and fasting, one hour, two and three hours post-load evaluation was then carried out, within two weeks, to the women who had a positive glucose challenge test (glucose value ≥140 mg/dl one hour after load). GDM was diagnosed when two or more glucose values were equal or exceeded the established cutoffs (95, 180, 155, and 140 mg/dl for fasting, 1, 2, and 3-h after load, respectively) according the Carpenter and Coustan suggestion [15]. However, although this test should be proposed to all pregnant women only a low percentage of patients are usually screened. A recent population-based study [26] showed how in Lombardy, an Italian region, the proportion of pregnancies with at least one screening test for GDM between 2007 and 2010 was only 30%. This proportion increased slightly from 2007 (27%) to 2010 (33%) and varied widely across local health management organizations of residence. Authors found also that socioeconomic indicators such as education, immigrant status, obstetric history, and pre-pregnancy hypertension were independent predictors of GDM screening. The study findings highlighted the need for programs to improve training of healthcare professionals, to raise women's awareness of GDM and to eliminate barriers to GDM screening.

Different authors disproved the role of the two-steps method with a first glucose challenge test in correctly detecting GDM. An Italian study (2003) had demonstrated that the two-steps method determines a misunderstanding of the real percentage of GDM. In this study, a diagnostic OGTT (100 g–3 h) was performed to a group of pregnant women with a negative glucose challenge test. Authors found that 6.3% of these women were affected by GDM [27] with an estimated prevalence for the whole cohort up to 12.3%.

In our country the new criteria (IADPSG) were quickly accepted in a National Consensus in March 2010 where the members of the two most important scientific society, Italian Society of Diabetes (SID), and Medical Association of Diabetologists (AMD) both decided to subscribe to these new criteria and therefore trying to adhere to an universally accepted diagnostic criteria for GDM. Only 18 months later the National Institute of Health reevaluated this position and mainly on the basis of a Cochrane meta-analysis [28], stated that "there was insufficient evidence to determine if universal

screening for gestational diabetes, or what types of screening, can improve maternal and infant health outcomes." With this persuasion a new panel, formed by the same scientific societies joined with members of National Institute of Health and CeVEAS (Centro per la valutazione dell'efficacia dell'assistenza sanitaria), proposed in 2011 the Italian Guidelines for the Physiological Pregnancy [29]. The document recommends a risk factor-based screening with a diagnostic 75 g–2 h OGTT to be performed only to women with risk factors. A first risk factors evaluation should be performed at 16–18 weeks gestation in order to detect women with high risk of developing GDM. The higher risk factors included are: pre-pregnancy BMI (calculated on the basis of the reported pre-pregnancy weight) $\geq$30 kg/m^2 and previous GDM or fasting glucose performed within the first trimester of pregnancy between 100 and 126 mg/dl. In the case of a negative OGTT result, women should repeat the diagnostic test at 24–28 weeks gestation. Also, at this gestational age women with family origin from areas with high diabetes prevalence, age $\geq$35 years, family history of type 2 diabetes, having a previous infant with macrosomia, and BMI $\geq$25 kg/m^2 have to undergo the diagnostic OGTT (Fig. 9.1).

Performing a risk factor-based screening could be cost-effective compared to universal screening. The question is: how many women with GDM would be lost at diagnosis and consequently not treated by risk factors-based screening?

The answer came few years later when a retrospective study was performed with the aim to compare in the same population the two diagnostic methods [2]. This study involved 1015 pregnant women consecutively referred to the Clinic of Diabetes and Pregnancy of the Department of Maternal Fetal Medicine of the University of Messina (Italy) from May 2010 to October 2011 for an oral glucose tolerance test (75 g–2 h) performed between 24 and 28 weeks of gestation.

All the data collected from these pregnant women were registered into a database that contained all the risk factors considered by the National Institute of Health Guidelines for each patient and later was completed to include delivery data. Among the eligible 1015 pregnant women who performed the diagnostic OGTT, GDM was diagnosed in 113 cases with a population prevalence of 11%. Of the 113 cases of GDM, 87 had one or more risk factors suggested by the National Institute of Health

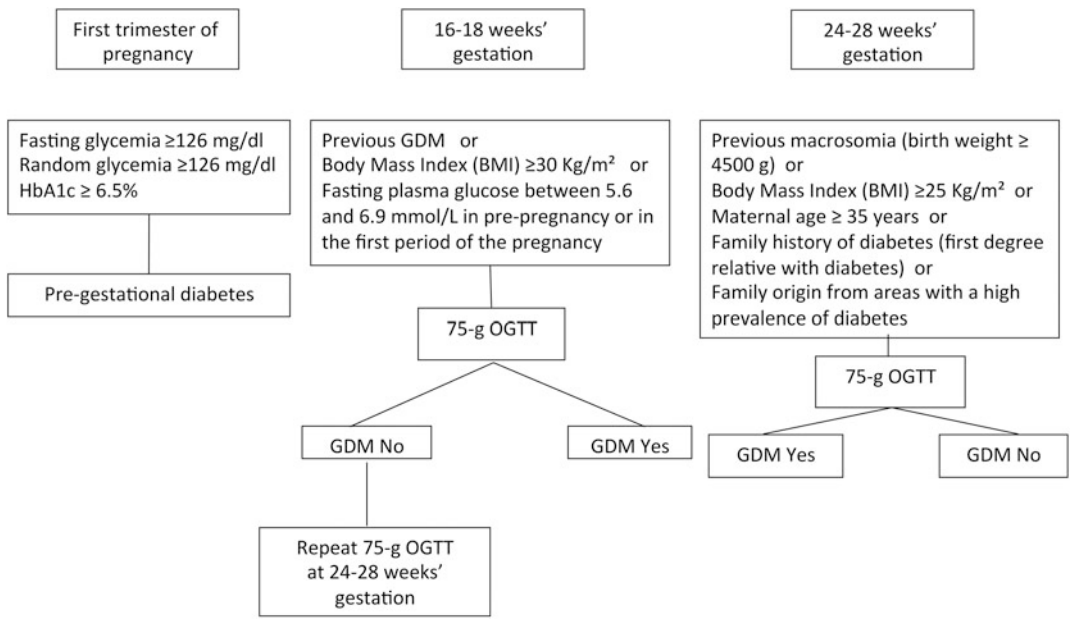


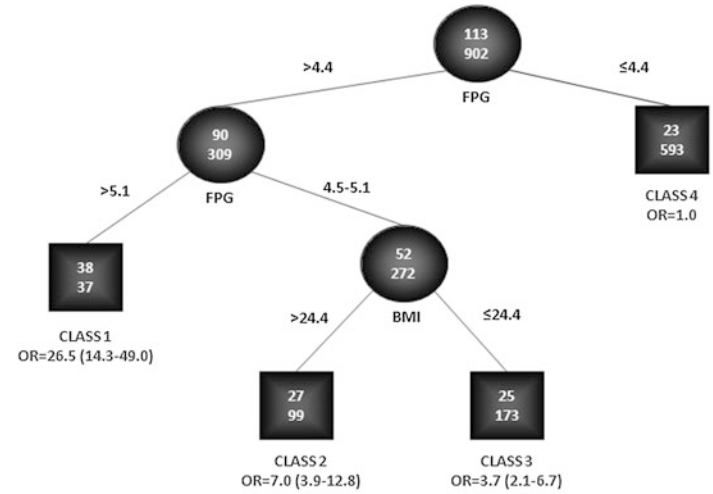
Fig. 9.1 Italian National Institute of Health Guidelines for Gestational Diabetes diagnosis

Guidelines, while 26 had no risk factors and would therefore have been undiagnosed. Therefore, according to the suggested guidelines 424 women should not undergo the OGTT and from that we could calculate a certain amount of saved money for each of those patients. When multivariate analyses were performed in order to detect the predictive role of each risk factor for GDM, every risk factor considered was associated with GDM development except age ≥35 years. The most relevant was the previous GDM which had a complete recurrence.

Another study performed in the North of Italy from January 2012 to December 2013, gave similar results [3]. From a cohort of 2552 consecutive pregnant women who underwent the screening for GDM (OGTT 75 g–2 h) 279 cases of GDM were diagnosed with a prevalence very close to 10.9%. It also confirmed the higher detection rate for the high risk factors (previous GDM, AGT and BMI ≥30) with an incidence of GDM in this group around 30%. The other risk factors (age ≥35 years, pre-pregnancy BMI ≥25 and ≤29.9, family history of a first-degree relative of type 2 diabetes, having a previous infant with macrosomia, or belonging to a high risk population race) had an incidence of GDM in this group of 13.7%. In the group, where no risk factors were diagnosed, only four GDM cases of the 98 pregnant low risk women screened were diagnosed.

Knowing what the independent predictive value of the risk factors for GDM established by selective screening represents is a useful tool. It is also important both for clinical practice and for healthcare planning, to know what subgroups of women are at a higher risk of developing GDM. With the aim of defining and more deeply investigating the characteristics of subgroups of women at high risk a study [30] was performed on a large sample of women (n = 1015) who underwent to universal screening according to the IADPSG recommendations. First, the study retrospectively applied the selective screening criteria to this population to estimate the number of OGTTs that would have been required by these selective criteria and the proportion of diagnoses of GDM that would have been missed. Second, the usefulness of a particular statistical tool, the tree-growing regression technique, in identifying distinct and homogeneous subgroups of patients at a higher risk of developing GDM was tested. Particularly, the RECursive Partitioning and AMalgamation (RECPAM) method was used. This method has been previously used in several studies in the field of diabetes. In this study it was used for the first time in the context of a study involving women with GDM. This tree-based method has some features that allow it to better explore the role of specific factors in determining risk. With the use of this technique the authors were able to identify subgroups of women at higher risk. The most important variable for differentiating the risk of GDM was represented by fasting plasma glucose (FPG). Women with a FPG value lower than 4.4 mmol/l had the lowest GDM prevalence, therefore representing the reference category (OR = 1.0). On the opposite side of the regression tree, patients with a FPG value higher than 5.1 mmol/l represented the subgroup of women with the highest prevalence of GDM, therefore having a high risk of developing this condition (OR 26.5; 95% CI 14.3–49.0). In women with FPG values between 4.5 and 5.1 mmol/l, the risk of GDM was further differentiated on the basis of pre-pregnancy BMI values. Women with a pre-pregnancy BMI higher than 24.4 kg/m2 had a higher risk of developing GDM (OR 7.0; 95% CI 3.9–12.8) that was almost double compared with women with a pre-pregnancy BMI lower than 24.4 kg/m2 (OR = 3.7; 95% CI 2.1–6.7). A notable point is that none of the other risk factors included in the model (that were the factors considered by the Italian recommendation) resulted in a determinant of distinct subgroups at increased risk of developing GDM (Fig. 9.2).

Finally, the authors compared the yield of the selective screening criteria strategy with that of an alternative approach, based on the risk stratification derived from the application of tree-growing regression techniques. In particular the authors tested the combination of different risk factors from the RECPAM model in a sensitivity analysis comparing them with selective and universal screening criteria. A screening strategy based on the most predictive risk factors suggested by the RECPAM model (i.e., FPG > 4.4 mmol/l or pre-pregnancy BMI > 25 kg/m2 or family history of diabetes) would result in saving 36.8% OGTTs, when compared with the universal screening criteria and would



Variable					P-value
Age (years)	32.0 (29.0-36.0)	32.0 (28.0-35.0)	31.0 (28.0-35.0)	30.0 (27.0-34.0)	<0.0001
Gestational age (weeks)	25.0 (24.0-28.0)	25.0 (24.0-27.0)	26.0 (25.0-27.0)	26.0 (25.0-27.0)	0.0399
Pre-pregnancy BMI (kg/m²)	25.9 (22.0-31.5)	27.3 (25.4-30.5)	21.7 (20.1-23.1)	22.5 (20.3-25.0)	<0.0001
Pre-pregnancy BMI ≥ 25 kg/m² (%)	58.7	82.5	0	24.5	<0.0001
Family history of diabetes (%)	49.3	31.8	18.7	21.3	<0.0001
Parity >1 (%)	56.0	54.0	42.9	46.0	0.0903
Previous GDM (%)	2.7	0.8	2.0	0.5	0.1134
Previous macrosomia (%)	6.7	4.0	0.5	1.1	0.0007
FPG between 100 and 125mg/dl (%)	17.3	0	0	0	<0.0001
FPG at first trimester (mmol/L)	5.3 (5.2-5.4)	4.8 (4.7-4.9)	4.7 (4.6-4.8)	4.2 (3.8-4.3)	<0.0001
Glycemia T0 at the OGTT (mmol/L)	4.9 (4.6-5.2)	4.6 (4.3-4.8)	4.4 (4.1-4.7)	4.3 (4.1-4.5)	<0.0001
Glycemia T60 at the OGTT (mmol/L)	9.2 (7.9-10.3)	7.1 (6.2-8.2)	6.9 (5.9-8.0)	6.7 (5.7-7.7)	<0.0001
Glycemia T120 at the OGTT (mmol/L)	7.2 (6.2-8.3)	5.9 (5.1-7.3)	5.8 (4.9-6.7)	5.8 (5.1-6.6)	<0.0001

Fig. 9.2 Identification of subgroups at different risks for GDM: results of RECPAM analysis. REPCAM analysis identified patient subgroups at different risks for GDM. The tree-growing algorithm modeled odds ratios (ORs) following a logistic regression with age, familiarity history of diabetes, fasting plasma glucose (FPG), pre-pregnancy Body Mass Index (BMI), previous macrosomia as global variables. Splitting variables are shown between branches, whereas a condition sending patients to left or right sibling is on a relative branch. Class 4 with lowest risk for GDM was the reference category (OR = 1). *Circles* indicate subgroups of patients; *squares* indicate the patient subgroup REPCAM class. Numbers inside *circles* and *squares* represent the number of events (*top*) and the number of nonevents (*bottom*), respectively. An odds ratio (OR) with the corresponding 95% CI (in parentheses) is attached to each class. The table placed at the bottom of the figure shows patients' characteristics within each RECPAM class (adapted from Ref. [30])

reduce by over 50% the number of undiagnosed GDM cases when compared with the selective screening approach, at the expense of a small number of additional OGTTs.

RECPAM lead to two incredible results mainly deriving from the power of the algorithm to choose the natural cutoff points of continuous variables. Specifically, the highest risk of developing GDM was observed in the subgroup of women with a FPG value >5.1 mmol/l, and this is exactly in line with the FPG diagnostic cutoff value proposed by the IADPSG. The lowest risk of developing GDM was observed in the subgroup of women with a FPG value <4.4 mmol/l, and this was surprisingly the same FPG cutoff value below which a sub-analysis of the HAPO Study showed a low risk of some adverse outcomes.

Apart of its complexity in the analytical phase, the study can offer some suggestions for the interpretation of the debate on universal or selective screening for GDM. Probably the truth is in the middle. One of the problems of the universal screening can be the extension of diagnostic procedures to subjects not requiring them. On the other part the evidence that a FPG <4.4 mmol/l is associated with the lowest risk for GDM onset holds a part of the population potentially at risk because of the

presence of FPG between 4.4 and 5.1 mmol/l. The risk factors-based selective screening can be limited by the presence of one or more risk factors that are not really predictive of GDM, resulting in a wrong selection of cases not at risk. With our RECPAM-based risk factors selection, we have showed that an effective and potentially cost-effective screening procedure can be used.

Given the presence of a risk factor-based screening for GDM in Italy, a check for the degree of diffusion and acceptance of the national guideline was performed [31]. This was needed also in order to detect possible areas for benchmarking. In 2013 the Italian Diabetes in Pregnancy Study Group promoted a national survey, focused on GDM screening and diagnostic procedures. In Italy the care of women with GDM takes place in dedicated specialist centers. Information on all major centers disseminated across the whole country involved in the care of GDM was collected. To ensure adequate consistency of data, only diabetes centers caring more than 30 women with GDM per year were considered. The survey was administered only to diabetologists. It also contains information on screening and diagnostic procedures made by obstetricians/gynecologists that was reported by diabetologists at the same center in which the obstetricians/gynecologists worked. A large number of respondents was registered, 122 diabetologists of 122 different diabetic centers of all the Italian regions completed the questionnaire. The wide national dissemination level of the survey was reached thanks to the contribution of the two main Italian Scientific Societies (Associazione Medici Diabetologi, AMD; Società Italiana di Diabetologia, SID) that sent it to all their members. Most of the respondent centers were hospitals or universities, almost one out of five being territorial centers. Among the answers it is interesting to note that the specialist who managed screening and diagnostic procedures was declared to be a diabetologist or a gynecologist in 25.3 and 17.2% of the cases, respectively. In the majority of the centers (57.6%) there was a diabetologist with the collaboration of an obstetricians/gynecologist. In the latter case, diabetologists and obstetricians/gynecologist could have the same (45.5%) or a different (12.1%) approach. Among healthcare professionals adopting the same approach only 13.7% were territorial, the remaining working in hospitals. The different approach faced with the same problem can lead to mistrust for both diabetologists and obstetricians/gynecologists on the part of women. This can be the case for example of women who have GDM in two different pregnancies and are cared for by two different healthcare professionals, with two different ways of care. Additionally, some legal problems may occur in these cases. With respect to the question on screening procedure if a selective risk factors-based or universal approach was adopted, was asked on the survey. Overall, in 82% of the cases a selective risk factors-based screening was preferred. Almost all the territorial centers declared to execute a selective screening, while only 77.7% of hospital and universities followed a similar procedure. One of the most relevant reasons was probably the difference in attitudes to execute the OGTT in the case of FPG $\geq$5.1 mmol/l (92 mg/dl). Two third of respondents used to proceed with the execution of the complete diagnostic OGTT, the others considering sufficient the FPG value $\geq$5.1 mmol/l (92 mg/dl) for the diagnosis. The Italian guideline recommends a first assessment at the 16–18 weeks gestation and in the case of the presence of at least one established risk factor to perform an early diagnostic 75 g OGTT. There was a specific question in the survey exploring the gestational age when the OGTT is usually performed in patients at high risk. Possible answers for this question were: as soon as possible, 16–18 weeks gestation, 24–28 weeks gestation. Overall, 84% of respondents were adhering to the indications of the guideline, others preferring to anticipate the OGTT as soon as possible (6.5%) or postponing it at 24–28 weeks gestation (9.5%). Accordingly, the survey allowed to recognize some criticisms, mainly linked to the choice of universal or risk factor-based screening, and to the right timing for executing the OGTT in women at high risk. The latter can depend on the personal experience of healthcare professionals in managing GDM. Anticipating the OGTT before the 16–18 weeks gestation can be an expression of increased worry by providers in the clinical management of women potentially at risk for GDM. On the opposite end, postponing the OGTT can be typical of specialists who do not feel that GDM is a very important condition or do not consider only high blood glucose values as determining a high risk status. As a result of the survey the need of

benchmarking activities to avoid heterogeneity in the application of the national recommendations was recognized. An element reinforcing this need is the evidence coming from the result of a lack of shared guidelines reported by 18% of respondents in the additional open field used for comments or problems the questionnaire contained. Great attention should be given to this national heterogeneity by the part of both healthcare providers and stakeholders.

Recommendations and Guidelines

The diagnosis of gestational diabetes in Italy by a risk factor selective screening was performed with a 75 g–2 h oral glucose tolerance test to the pregnant women with one or more risk factors. After the exclusion of preexisting diabetes during the first trimester of pregnancy (fasting glycemia $\geq$126 mg/dl, random glycemia $\geq$200 mg/dl and glycated hemoglobin $\geq$6.5%) at 16–18 weeks of gestation the OGTT should be performed in pregnant women with the higher risk factors as BMI $\geq$30, previous GDM or AGT in the first trimester of pregnancy. Those with a negative test should have a repeat OGTT performed between 24 and 26 weeks of gestation age. Women who should also receive an OGTT at this gestational age include those with family origin from areas with high diabetes prevalence, age $\geq$35 years, family history of type 2 diabetes, having a previous infant with macrosomia, BMI $\geq$25 kg/m2 (Fig. 9.1). The OGTT is evaluated according to the IADPSG panel criteria.

These are the Guidelines of the Italian National Institute of Health.

Conclusion

The social relevance of GDM has been recognized worldwide by all healthcare systems. The diagnosis of this condition is characterized by the longstanding debate on the utility of universal versus selective screening procedure. A risk factors-based screening has its rationale in considering cost-effectiveness of testing for GDM in all pregnant women belonging to a population at low risk of developing GDM. Consequently, the choice of different risk factors could lead to different approaches with the result of poor sensitivity and specificity. A universal diagnostic procedure is now promoted by major scientific societies such as WHO, IDF, FIGO, and others. Both the problem of risk factors selection and the extension of screening procedure to all pregnant women point out the lack of good evidence to support cost-effectiveness. Having reliable information on the cost and cost-effectiveness of GDM screening and treatment would facilitate decision-making. Almost all cost-effectiveness analyses have assessed only short-term complications [32]. However the main GDM-relevant long-term complication is type 2 diabetes development late in life. A recent study, based on the Gestational Diabetes Formulas for Cost-Effectiveness (GeDiForCE) Model [33] showed that the intervention on GDM is highly cost-effective when long-term effect is taken into account. In Italy, a study evaluating the cost-effectiveness of GDM screening has not been performed, this constituting future area of research. The effect of following current Italian guideline should be evaluated taking into account economic aspects also. Stakeholders should reconsider the included risk factors for GDM if a selective screening approach would be continued. The role of mothers' age and the cutoff of blood glucose values should be reassessed as showed by recent papers. Other risk factors different than those already foreseen by guideline, such as PCOS, could be considered. Risk models based on epidemiological data and population-based cohorts could represent future perspectives for the solution of the dilemma of finding the best screening procedure for GDM.

Acknowledgements D'Amico Angela, MD, for a critical reading of the whole manuscript and the grammar and English corrections.

References

1. Metzger BE. Summary and recommendations of the third international workshop conference on gestational diabetes. Diabetes 1991;40:197–201.
2. Corrado F, Pintaudi B, Di Vieste G, Interdonato ML, Magliarditi M, Santamaria A, et al. Italian risk factor-based screening for gestational diabetes. J Matern Fetal Neonatal Med. 2014;27(14):1445–8.
3. Lacaria E, Lencioni C, Russo L, Romano M, Lemmi P, Battini L, et al. Selective screening for GDM in Italy: application and effectiveness of national guidelines. J Matern Fetal Neonatal Med. 2015;28(15):1842–4.
4. Blank A, Grave G, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed: report of the International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes Mellitus. Diabetes Care. 1995;18:127–9.
5. Kjos SL, Buchanan TA. Gestational diabetes mellitus. N Engl J Med. 1999;341:1749–56.
6. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, Damm P. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes Care. 2008;31:340–6.
7. Bellamy L, Casas JP, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373:1773–9.
8. Yuhong X, Shutong S, Lizhou S, Haiwei Y, Bai J, Xiaohui C. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS One. 2014;9(1):e87863.
9. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care. 2007;30 (Suppl 2):S169–74.
10. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group* Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352:2477-86.
11. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361:1339–48.
12. Coustan DR. Diabetes mellitus in pregnancy: principle and practice. New York: Churchill Livingstone; 1998.
13. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes. 1964;13:278–85.
14. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979;28:1039–57.
15. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;161:638–41.
16. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2000;23:S77–9.
17. Word Health Organization report. Diagnosis and Classification of Diabetes Mellitus Geneva; 1998.
18. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002.
19. International Association of Diabetes and Pregnancy Study Groups (IADPSG). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33:676–82.
20. American diabetes association standard of medical care in diabetes. 2011;34(Suppl 1):S11–61.
21. VanDorsten JP, Dodson WE, Espeland MA, Grobman WA, Guise JM, Mercer BM, et al. Diagnosing gestational diabetes mellitus. Nat Inst Health Consensus State Sci Statements. 2013;29(1):1–30.
22. ACOG Practice bullettin n.137. gestational diabetes. 2013;122(2):406–416.
23. Lapolla A, Dalfrà MG, Lencioni C, Di Cianni G. Epidemiology of diabetes in pregnancy: a review of Italian data. Diabetes Nutr Metab. 2004;17:358–67.
24. Corrado F, D'Anna R, Cannata ML, Caputo F, Rizzo P, Cannizzaro D, et al. Prevalence of risk factors in the screening of carbohydrate intolerance in pregnancy. Nutr Metab Cardiovasc Dis. 2006;161:79–80.
25. American Diabetes Association. Standards of medical care for patients with diabetes mellitus diabetes care 2002;25 (Suppl.1):S33–49.
26. Nicotra F, Molinari C, Dozio N, Castiglioni MT, Ibrahim B, Zambon A, et al. Screening for gestational diabetes in the Lombardy region: a population-based study. Diabetes Metab. 2015;41(4):319–25.
27. Di Cianni G, Volpe L, Lencioni C, Miccoli R, Cuccuru I, Ghio A, et al. Prevalence and risk factors for gestational diabetes assessed by universal screening. Diabetes Res ClinPract. 2003;62(2):131–7.

28. Tieu J1, Middleton P, McPhee AJ, Crowther CA. Screening and subsequent management for gestational diabetes for improving maternal and infant health. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD007222.
29. Sistema Nazionale Linee Guida (SNLG-ISS). Linee guida su gravidanza fisiologica aggiornamento; 2011:169–73.
30. Pintaudi B, Di Vieste G, Corrado F, Lucisano G, Pellegrini F, Giunta L, et al. Improvement of selective screening strategy for gestational diabetes through a more accurate definition of high-risk groups. Eur J Endocrinol. 2013;22 (170):87–93.
31. Pintaudi B, Fresa R, Dalfra` M, Marcone T, Dodesini AR, Napoli A, et al. Level of implementation of guidelines on screening and diagnosis of gestational diabetes: a national survey. Diab Res ClinPract. 2016;113:48–52.
32. Poncet B, Touzet S, Rocher L, Berland M, Orgiazzi J, Colin C. Cost-effectiveness analysis of gestational diabetes mellitus screening in France. Eur J Obstet Gynecol Reprod Biol. 2002;103(2):122–9.
33. Lohse N, Marseille E, Kahn JG. Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. Int J Gynecol Obstet. 2011;115(Suppl 1):S20–5.

Part IV
Genetic and Molecular Factors Associated with Maternal Gestational Diabetes

Chapter 10
Metabolic Fingerprints of Gestational Diabetes Mellitus

Danuta Dudzik, Coral Barbas and M. Pilar Ramos

Key Points

- Gestational Diabetes Mellitus (GDM) is increasing worldwide. Although diabetes usually remits after pregnancy, women with gestational diabetes have a high risk of developing postpartum type 2 diabetes, particularly when accompanied by obesity. A better understanding of gestational diabetes pathophysiology is required for the identification of potentially modifiable risk factors and early prognostic markers for this disease.
- Current "omics" techniques, in particular metabolomics, provide deeper insights into disease-related metabolic alterations and provide useful information for the discovery of biomarkers.
- Plasma metabolic fingerprints reveal disease-specific metabolic imbalances, indicative of low-grade inflammation and an altered redox-balance that may reflect on the specific pathophysiological context of gestational diabetes.
- Various metabolites, such as lysoglycerophospholipids, fatty acids, 2-hydroxybutyrate, 3-hydroxybutyrate, and some amino acids, reflect on glucose intolerance in gestational diabetes.
- These findings highlight the potential use of GDM-related metabolites as prognostic markers for the identification of women at risk to develop severe glucose intolerance during pregnancy or to predict the risk of postpartum diabetic complications.

Keywords Gestational diabetes mellitus · Maternal metabolism · Metabolic fingerprinting · Metabolomics · Fingerprints

Abbreviations

AA	Amino acids
BCAAs	Branched-chain amino acids
CE	Capillary electrophoresis
FA	Fatty acid

D. Dudzik · C. Barbas
Facultad de Farmacia, CEMBIO (Center for Metabolomics and Bioanalysis),
Universidad CEU San Pablo, Ctra. Boadilla del Monte km 5.3, Madrid 28668, Spain
e-mail: danuta.dudzik@ceu.es

C. Barbas
e-mail: cbarbas@ceu.es

M.P. Ramos (✉)
Biochemistry and Molecular Biology, Facultad de Farmacia, Universidad CEU San Pablo,
Ctra. Boadilla del Monte km 5.3, Madrid 28668, Spain
e-mail: pramos@ceu.es

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_10

GC	Gas chromatography
GDM	Gestational diabetes mellitus
IGT	Impaired glucose tolerance
LC	Liquid chromatography
LPC	Lysophosphatidylcholines
LPE	Lysophosphatidylethanolamine
MS	Mass spectrometry
MW	Molecular weight
NADH	Reduced nicotinamide adenine dinucleotide
NEFA	Non-esterified fatty acids
NMR	Nuclear magnetic resonance
PC	Phosphatidylcholine
TCA	Tricarboxylic acid cycle

Introduction

Gestational Diabetes Mellitus (GDM), defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" is increasing worldwide and is a common metabolic abnormality encountered in routine obstetric practice. Despite advances in diagnosis and good maternal control, a significant increase in obstetric morbidity is associated with GDM as a consequence of short- and long-term health complications for the mother, the foetus and the neonate. Although diabetes usually remits after pregnancy, women with GDM have a high risk of developing postpartum type 2 diabetes (T2DM), particularly when accompanied by obesity.

There is a lack of international uniformity regarding the ascertainment and diagnosis of GDM. Therefore, understanding the pathophysiology of GDM, as well as the identification of potentially modifiable risk factors and early diagnostic markers for GDM, are relevant issues. Contemporary "omics" approaches are a powerful tool to gain deeper insights in the etiopathogenesis of the disease and biomarkers discovery.

Metabolomics Applied to GDM

Metabolomics (see Table 1, Fig. 1) adds to previously developed omics platforms (genomics, transcriptomics, and proteomics) the study of the whole set of small molecules (MW < 1000 Da) that are produced by a biological system and represent the final outcome of gene expression, transcription, and post-translational modifications. Therefore, metabolites are the compounds closer to the phenotype and change more intensely and more quickly after an insult. Metabolites have a broad range of physic-chemical properties and concentrations, and there is not one simple way to analyse all of them simultaneously. In practice, metabolomics is performed in two ways: targeted and non-targeted analysis.

Targeted metabolomics uses specific, quantitative methods for selected groups of compounds, therefore, its main advantage is that compounds are identified and quantified with accuracy. Its disadvantage in a discovery phase is the limitation to a maximum of several hundred metabolites and the fact that requires an *a priori* hypothesis. Non-targeted metabolomics involves the comparison of profiles, as broad and non-biased as possible, of at least two groups (cases and controls), applying

Table 1 Omics-related definitions

	Definition
Systems biology	Systematic study which integrates the information at different levels/systems (genomics, transcriptomics, proteomics, metabolomics) in order to provide complex molecular insight in the organism being studied [54]
Metabonomics	Quantitative measurement of the dynamic multi-parametric metabolic response of living systems to pathophysiological stimuli or genetic modification [55]
Metabolomics	Unbiased identification and quantification of the complete set of metabolites present in a biological system (cell, tissue or organism) under a given set of conditions [56, 57]
Metabolome	Complete set of metabolites present in cells in a particular physiological or developmental state. The metabolome is environment dependent, dynamic and undergoes constant changes [57]
Metabolites	Low molecular weight compounds which are the reactants, intermediates or products of enzyme-mediated biochemical reactions (including hormones and signaling molecules) that represent the ultimate response of a biological system to genetic and environmental changes [57]
Metabolic fingerprinting	Untargeted approach that aims to define changes in whole metabolome at the specific state in a cell, tissue or organism without a priori identification of biologically interesting metabolites. A unique and disease-specific metabolite pattern or "fingerprint" allows for mapping the metabolome, deciphering biological processes, and identification of compounds that change in response to a disease, pharmacological therapies or environmental alterations [1, 5]
Metabolic profiling	Focused on a specific group of metabolites e.g. amino acids, or metabolites associated with a specific metabolic pathway [58]
Targeted analysis	Quantitative determination of one or a few metabolites related to a specific metabolic pathway. Methods with high selectivity and sensitivity are applied, and it requires appropriate sample preparation. Absolute quantitation is performed by the incorporation of internal standards [59]
Untargeted analysis	Global in scope with the aim to simultaneously measure as many metabolites as possible from biological samples without bias. The metabolites to be identified are not known before study and experiments are referred as "hypothesis generating" [2]

differential analysis to find potential markers of the condition under study. Those markers can permit to elaborate new hypothesis about the pathological mechanism.

Metabolomics is mainly performed with two analytical platforms [1]: nuclear magnetic resonance (NMR) and mass spectrometry (MS); the latter is coupled to different separation techniques: liquid chromatography (LC); gas chromatography (GC) and capillary electrophoresis (CE). NMR requires minimal manipulation of the samples, is robust and reproducible, whereas MS approaches vary depending on the technique used for the previous separation of the sample. MS coupled to GC requires sample derivatization to produce volatile compounds and it can detect small molecules such as amino acids (AAs), short-chain fatty acids (FAs) and simple carbohydrates. Using MS coupled to LC, medium and non-polar compounds can be detected (mainly lipids); with MS coupled to CE, ionic and ionizable compounds can be measured, which suits very well for urine and amniotic fluid components. MS provides a strong advantage in sensitivity compared to NMR, and via application of different combinations of chromatographic methods and mass/charge separation technologies, allows the measurement of a broader array of small molecules or metabolites.

Both types of analysis can be used with two different but not exclusionary ways: identification of novel biomarkers for diagnostic purposes and/or identification of altered pathways to gain mechanistic insights. The identification of diagnostic markers requires the determination in a broad cohort and the corresponding validation; most of the studies fail at this point [2–5].

A growing number of metabolomics studies aimed at uncovering the metabolic signature of T2DM, focus on potential biomarkers of altered glucose tolerance and onset of insulin resistance,

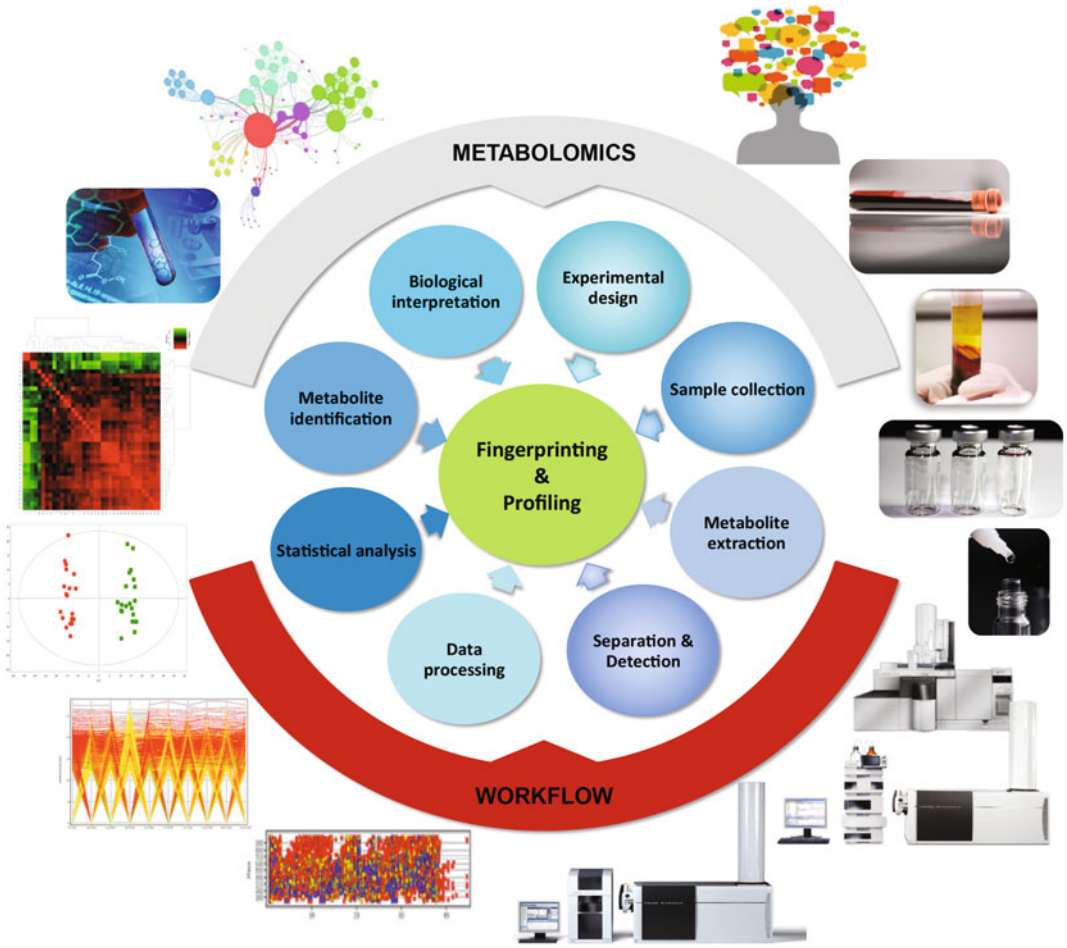


Fig. 1 Workflow of metabolomics analysis

such as acylcarnitines, choline-containing phospholipids, branched-chain amino acids and 2-hydroxybutyrate [6, 7]. Analytical problems are frequent, such as differences in protocols, instrumentation, lack of standardization or different statistical approaches. Therefore, it is difficult to compare results from different studies and sometimes the results are contradictory [8]. Nonetheless, metabolomic studies have the potential to determine sets of metabolites that are predictive of both prediabetes and T2DM, even before the onset of disease, and this can contribute improving patients' health, as shown recently for T2DM [9]. Thus, although there is much work left to do, the evidence of metabolomics benefitting T2DM care makes its clinical application inevitable and this is extensible to GDM.

The application of metabolomics-based approaches to the study of GDM is still limited, and in some cases has yielded inconsistent results [10–26]. There are several limitations that must be considered, such as small sample size, differences in the GDM diagnostics criteria, variability in the cohort due to the age, gestational week, treatment or other factors. Experimental variations and methodological differences across studies should also be carefully evaluated. Notwithstanding, metabolomics and, in particular, global untargeted analysis has a great potential to provide novel insights into molecular mechanisms underlying disease onset, monitor disease progression and identify clinically relevant biomarkers. Metabolomics approaches were used in the analysis of plasma

[14, 18, 22, 23, 25], serum [12, 17, 19–21, 26], urine [10, 14–16, 18, 23, 24] and amniotic fluid samples [11, 13, 15]. The majority of GDM-related metabolomics studies were based on proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy [10, 11, 13, 14, 16, 25] and GC/MS metabolite profiling [12, 17, 19, 21, 24]. A global, multiplatform (LC/MS, GC/MS and CE/MS) analysis for wide metabolite coverage has been provided only by our group [18]. The overview of related studies is provided in Table 2. In 1994, the first study on amniotic fluid analysis was published. However, probably due to the very low sample size (n = 5 GDM), no significant changes were found [11]. A case-control study with the population of 49 GDM, 80 impaired glucose tolerance (IGT) but not-GDM subjects and 98 controls has linked circulating non-esterified fatty acids (NEFA) to dietary fat intake in women with GDM [12]. The authors found a graded relationship between the severity of maternal hyperglycemia and concentration of individual NEFAs at both the beginning and the third trimester of gestation [12]. They described an increase, during the third trimester, of total and individual NEFA, including myristic, palmitic, palmitoleic, oleic, linoleic, linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acids. Similar relationships were observed in the second trimester with regard to total NEFAs and myristic, palmitic, palmitoleic and eicosapentaenoic acids [12]. Subsequent untargeted studies also linked NEFAs, in particular palmitic, oleic, linoleic and myristic acids, with GDM pathogenesis [18, 19, 21].

Several studies have reported that the plasma and serum concentrations of aromatic and branched-chain amino acids (BCAAs) are significantly altered in diabetes, and they are closely correlated to insulin resistance and hyperglycemia [27, 28]. Scholters et al. observed elevated serum levels of BCAAs, including leucine, isoleucine and valine, in women with high fasting plasma glucose in ~28 weeks of pregnancy [19]. Recently, elevated valine concentrations were also described when untargeted GC/MS was performed in serum to track early metabolic changes in pregnancy using a representative sample cohort (178 GDM cases and 180 controls) [21]. However, the results are inconsistent with others; Hajduk et al. found decreased valine concentration in fasting plasma in weeks 24–28 of pregnancy [23], and Pinto et al. found increased valine in prediagnostic GDM (16–21 week), but reduced levels in weeks 24–27 of gestation after GDM diagnosis [25]. Nonetheless, these studies were performed on a low sample size and, keeping these limitations in mind, their results should be interpreted cautiously. Along with BCAAs, aromatic AAs, such as phenylalanine, tyrosine, histidine and tryptophan, have been implicated in the aetiology of GDM [18, 19, 24]. Recent studies have also revealed the utility of 2-hydroxybutyrate for predicting hyperglycemia in pregnancy [18, 19]. Interestingly, the elevation of ketone bodies in GDM was evidenced by increasing levels of 3-hydroxybutyrate, a product of acetoacetate metabolism derived from ketogenic AAs [18, 19]. We reported also alterations of the levels and composition of plasma lysophospholipids as the most prominent changes that correlated significantly with the glycemic state of pregnant women [18]. Many other metabolites and related biochemical pathways were found to be associated with the onset of GDM. However, these results have not been validated therefore, further studies in large and homogenous population are still needed.

Physiological Relevance of Data Obtained in Metabolomic Studies

During gestation, the mother undergoes many physiological changes in order to maintain the adequate conditions and metabolic fuels required for foetal development. Alterations or mal-adaptations of these physiological changes during pregnancy may cause health risks both in the mother and in the foetus. However, these changes are still relatively unexplored, especially those associated with GDM. Studies performed so far have mainly focused on targeted metabolites but not overall metabolite profiling of maternal plasma.

Table 2 Metabolomic approaches applied to study gestational diabetes mellitus

Population	Gestational age	Sample type	Diagnostics criteria	Technique	Main findings	Author, year
5GDM versus controls (number of samples not clearly specified)	2nd and 3rd trimester	Amniotic fluid	Unknown	^{1}H NMR	No statistically significant changes	Bock 1994 [11]
49 GDM, 80 IGT not-GDM versus 98 controls	Time-1: 16.5 ± 0.2 weeks, Time-2: 30.8 ± 0.2 weeks	Fasting serum	Carpenter–Coustan	Targeted GC-MS	**Time-1. Increase:** myristic, palmitic and total saturated FA, palmitoleic, eicosapentaenoic acids, total free FA **Time-2. Increase**: myristic, palmitic, stearic and total saturated FA, palmitoleic, oleic and total MUFAs; linoleic, linolenic, arachidonic, eicosapentaenoic, docosahexaenoic and total PUFAs	Chen et al., 2010 [12]
27 Pre-diagn. GDM versus 82 controls	14–25 weeks	Amniotic fluid	Unknown	^{1}H NMR	**Increase:** glucose **Decrease:** acetate, creatinine, formate, glutamate, glycine, proline, serine, taurine, glycerophosphocholine	Graca et al., 2010 [13]
14 Pre-diag. GDM versus 20 controls	Pre-diag. GDM: 16–22 weeks, Controls: 16–21 weeks	Plasma fasting	Unknown	^{1}H NMR	**Urine. Increase:** 3-hydroxyisovaleric and 2-hydroxyisobutyric acids, choline, N-methyl-2-pyridone-5-carboxamide, N-methyl-nicotinamide **Plasma. Decrease:** trimethylamine-N-oxide, betaine	Diaz et al., 2011 [14]
29 pre-diag. GDM versus 25 controls		Urine				
99 GDM versus 492 controls	V1: 8–20 week V2: 26–30 week	Urine	WHO	^{1}H NMR	**V1. Increase:** citric acid **V2. Increase:** citric acid	Sachse et al., 2012 [10]
239 GDM (G1, G2) versus 492 controls (G0)			IADPSG		**V1. Increase:** citric acid, lysine, glucose (G2) **V2. Increase:** citric acid, glucose (G2)	
20 Pre-diag. GDM versus 21 controls	Pre-diag. GDM: 16–21 weeks Controls: 16–22 weeks	Urine	Unknown	Untargeted LC-MS	No statistically significant changes	Graca et al., 2012 [15]
23 Pre-diag. GDM versus 26 controls		Amniotic fluid				

(continued)

Table 2 (continued)

Population	Gestational age	Sample type	Diagnostics criteria	Technique	Main findings	Author, year
42 Pre-diag. GDM versus 84 controls	Pre-diag. GDM: 16–22 weeks Controls: 15–26	Urine	Unknown	^{1}H NMR	**Increase:** choline, glucose, N-methylnicotinamide, xylose **Decrease:** 4-hydroxyphenylacetate, hippurate	Diaz et al., 2013 [16]
22 GDM versus 26 controls	20 weeks	Fasting serum	75 g OGTT (1) FG $\geq$ 5.5 mmol/l and/or 2 h $\geq$ 9.0 mmol/l or (2) 1 h > 11.0; no GTT available	Untargeted GC-MS	**Increase:** itaconic and cis-aconitic acids	de Seymour et al., 2014 [17]
20 GDM versus 20 controls	GDM: 25.5 ± 1.6 weeks Controls: 24.8 ± 1.3 weeks	Fasting plasma urine	WHO	Untargeted LC-QTOF/MS GC-Q/MS CE-TOF/MS	**Plasma. Increase:** glycerol, 2-hydroxybutyric, 3-hydroxybutyric, linoleic and fumaric acids **Decrease:** LPE(20:2), LPE(20:1), trihydroxy-cholestanoyl taurine, LPA(18:2), LPC(20:5), LPI(20:4), LPC(18:2), PC(21:1), LPC(18:1), LPE(22:4), LPS(20:0), LipoxinC4, LPC(22:5), LPC(22:4), LPI(18:2), LPC(20:2), LPC(20:4), taurolithocholic acid glucuronide, LPC(19:1), LPC(22:6), LPI(22:6), glycerophosphocholine, docosahexaenoic acid methylester, arachidonic acid methylester, LPI (20:3), LPE(18:2), LPE(20:4), LPE(22:6), creatinine, L-tryptophan, glycine, L-glutamic, pyruvic and lauric acids **Urine. Increase:** histidine, glutamine, phenylalanine, tryptophan, cystine **Decrease:** carnitine	Dudzik et al., 2014 [18]
67 High fasting plasma glucose (FPG) versus 50 Low FPG	High FPG: 28.3 ± 1.4 weeks Low FPG: 28.1 ± 1.5 weeks	Serum fasting	IADPSG	Targeted MS-AA analysis, untargeted GC-MS	**Increase:** proline, valine, alanine, glutamine/glutamate, arginine, leucine/isoleucine, asparagine/aspartate, phenylalanine, cis/trans-4-hydroxyproline, serine, ornithine, threonine, gluconic acid, glucose/aldohexoses, fructose/ketohexoses, threitol/tetritols, xylitol/pentitols, palmitic, lauric and heptadecanoic acids, α-tocopherol,	Scholtens et al., 2014 [19]

(continued)

Table 2 (continued)

Population	Gestational age	Sample type	Diagnostics criteria	Technique	Main findings	Author, year
					3-hydroxybutyric acid, acetoacetic acid, pyruvic acid, 2-ketoglutaric, 2-hydroxybutyric and isocitric acids, creatinine **Decrease:** 1-5-anhydroglucitol, manitol/hexitols, β-sitosterol	
96 GDM versus 96 controls	GDM: 10.4 ± 2.4 weeks Controls: 11.7 ± 3,4 weeks	Serum fasting	Carpenter–Coustan	Targeted LC-MS	**Increase:** anthranilic acid, alanine, glutamate, allantoin, serine **Decrease**: creatinine	Bentley-Lewis et al., 2015 [20]
178 GDM versus 180 controls	GDM: 15.6 ± 2.9 weeks Controls: 15.6 ± 2.9 weeks	Serum fasting	Carpenter–Coustan	Untargeted GC-MS	**Increase:** linoleic, oleic and myristic acids; D-galactose, D-sorbitol, L-alanine, L-valine, L-lactic acid, fumaric acid **Decrease:** O-phosphocolamine, 5-hydroxy-L-tryptophan, L-phenylalanine-phenyl, L-serine, sarcosine, L-mimosine, L-pyroglutamate, glycolic acid, urea	Enquobahrie et al., 2015 [21]
9 GDM versus 15 Controls	24–27 weeks	Fasting plasma 30 min, 120 mi - OGTT	IADPSG	Targeted FIA-MS/MS LC-MS	**Fasting. Decrease:** Diacyl-phosphatidylcholine (PC-aa) C36:4, LPC20:4 **30 min-OGTT**. **Increase:** C18:0-carnitine. **Decrease:** PC-aa C34:4, C36:4; LPC20:4 **120 min-OGTT**. **Increase:** C18:0-carnitine. **Decrease:** PC-aa C34:4, C36:4, C38:5; LPC20:4, C20:4 (arachidonic acid)	Lehmann et al., 2015 [22]
18 GDM versus 13 controls	24–28 weeks	Fasting plasma	WHO	LC-MS based AA profiling	**Increase:** citrulline **Decrease**: L-asparagine, valine, ornithine	Hajduk et al., 2015 [23]
20 GDM versus 20 controls	22–28 weeks	Urine	WHO	GC-MS AA profiling	**Increase:** D-phenylalanine	Lorenzo et al., 2015 [24]
32 Pre-diag. GDM, 12 Post-diag. GDM versus 49 controls	Pre-diag. GDM: 16–21 weeks Post-diag. GDM: 24–27 weeks Controls: 16–24 weeks	Fasting plasma lipid extracts	IADPSG	^{1}H NMR	**Prediagnosis GDM versus controls. Increase:** valine, pyruvic and lactic acids, glucose, C18H cholesterol, CH_3 lip. HDL, CH_3 lip. LDL + VLDL, $(CH_2)_n$ lip. HDL, $(CH_2)_n$ lip. LDL + VLDL, CH_2CH_2CO lip., $CH_2C = C$ lip., CH_2CO lip., $C = CCH_2C = C$ lip., N	Pinto et al., 2015 [25]

(continued)

Table 2 (continued)

Population	Gestational age	Sample type	Diagnostics criteria	Technique	Main findings	Author, year
					$(CH_3)_3$ chol. LDL + VLDL, HC = CH HDL, HC = CH LDL + VLDL, $(CH_2)_n/CH_3$ lip. HDL, HC = CH/CH_3 lip. HDL, $(CH_2)_2/CH_3$ lip. LDL + VLDL, HC = CH/CH_3 lip. LDL + VLDL **Decrease:** glutamine, creatine, dimethyl sulfone, trimethylamine-N-oxide, betaine, proline, 1,5 anhydroglucitol, urea, CH_3 HDL/CH_3 LDL + VLDL **Post-diag. GDM versus controls**. **Increase:** C18H cholesterol, CH_3 lip. HDL, CH_3 lip. LDL + VLDL, $(CH_2)_n$ lip. HDL, $(CH_2)_n$ lip. LDL + VLDL, CH_2CH_2CO lip., CH_2 = C lip., CH_2CO lip., C = CCH_2C = C lip., N $(CH_3)_3$ chol. LDL + VLDL, CH2-N$(CH_3)_3$ chol., glyceryl-Cl,3H, glyceryl-Cl,3H, HC = CH HDL, HC = CH LDL + VLDL, $(CH_2)_n/CH_3$ lip. HDL, HC = CH/CH_3 lip. HDL, $(CH_2)_n/CH_3$ lip. LDL + VLDL, HC = CH/CH_3 lip. LDL + VLDL **Decrease:** valine, alanine, pyruvic acid, glutamine, citrate, creatine, creatinine, dimethyl sulfone, trimethylamine-N-oxide, betaine, proline, metanol, glycine, lactate, glucose, N $(CH_3)_3$ choline HD, CH_3 HDL/CH_3 LDL + VLDL	
14 Pre-diag. GDM, 12 Post-diag. GDM versus 15 controls	Pre-diag GDM: 16–19 weeks Post-diag. GDM: 24–27 weeks Controls: 16–22 weeks				**Pre-diag. GDM versus controls**. **Increase:** FA: CH_3, $(CH_2)_2$, = $CHCH_2(CH_2)$n, CH_2CH_2CH =, CH_2CO, HC = CH 18:2 FA, HC = CH 20:4 FA. Free and esterified cholesterol (EC): $C_{18}H_3$ FC & EC, $C_{26}H_3$ FC&EC, $C_{19}H_3$ FC, $C_{19}H_3$ EC, C_4H_2 EC, C_3H EC. Triglycerides: glyceryl-CH_2, glyceryl-C_3H_2 **Post-diag. GDM versus controls**. **Increase:** FA: CH_3, $(CH_2)_2$, = $CHCH_2(CH_2)$n,	

(continued)

Table 2 (continued)

Population	Gestational age	Sample type	Diagnostics criteria	Technique	Main findings	Author, year
					CH_2CH_2CH =, CH_2CH = 18:2 FA, CH_2CO, = $CHCH_2CH$ = 18:2 FA, HC = CH 18:2 FA, HC = CH 20:4 FA, Free and esterified cholesterol (EC): $C_{18}H_3$ FC&EC, $C_{26}H_3$ FC&EC, $C_{19}H_3$ FC, $C_{19}H_3$ EC, C_4H_2 EC, C_3H EC. Triglycerides: glyceryl-CH_2, glyceryl-C_3H_2	
12 GDM versus 10 controls	GDM: 39.4 ± 1.0 weeks Controls: 38.6 ± 1.3 weeks	Fasting serum	IADPSG	Untargeted LC-QTOF/MS	**Increase**: 1-methyladenosine, homovanillic acid, *trans*-3-octenedioic acid, glucosamine, LPC(16:1), 3-methylthiopropionic acid, LPC (20:2), L-lactic acid, L-tyrosine, L-2-hydroxyglutaric acid, phosphorylcholine **Decrease:** gluconolactone, 3-methylhistidine, serinyl-glycine, LPC(20:4(5Z.8Z,11Z,14Z), 2-oxo-4-methylthiobutanoic acid, SM (d18:0/18:0), indoleacetaldehyde, PE (14:1/20:0), 3-oxooctadecanoic acid, glycine, pyridoxal, 3-methylhistidine, capric, stearic and arabinonic acids	Liu et al., 2016 [26]

AA amino acid; *FA* fatty acid; *FG* fasting glucose; *Pre-diag.* prediagnosis; *Post-diag*: postdiagnosis; *LPE* lysophosphatidylethanolamine, *LPA* lysophosphatidic acid, *LPC* lysoglycerophospholipid, *LPI* lysophosphatidylinositol, *LPS* lysophosphatidylserine, *PC* phosphatidylcholine, *SM* sphingomyelin, *PE* phosphatidylethanolamine

We have recently found that plasma metabolite fingerprints allow for a clear discrimination of women with normal glucose tolerance from those with GDM [18]. Therefore, the identification of a set of metabolites that correlate with glycemic control of the diabetic pregnant women should improve our understanding of GDM metabolism and may provide a basis for therapeutic strategies to prevent obstetric complications. Furthermore, alterations in maternal metabolism during pregnancy may also provide insights into the development of T2DM, for which these women are at a higher risk later in life. Figure 2 shows putative alterations of various metabolic pathways in the second trimester of gestation according to the identification of metabolites by metabolomics approaches (for details see Table 2).

Phospholipids

Both phospholipids and lysophospholipids are implicated in relevant biological functions, and they have been associated with inflammation [29] and metabolic alterations as T2DM. It has been reported that, during pregnancy, there is a physiological decrease in lysophospholipids, probably as a consequence of lower phospholipase activity or high consumption rate [30]. We and other groups have described that this metabolic adaptation of gestation is further exacerbated in GDM [18, 22]. Furthermore, alterations in both the level and composition of plasma lysophospholipids were the most prominent changes that correlated with the glycemic state of GDM pregnant women [18], in particular, some LPEs (lysophosphatidylethanolamines) and lysophosphatidylcholines, (LPC) as LPE (20:2) and LPC(18:2). LPE are bioactive metabolites and their anti-inflammatory action has been demonstrated in a mouse model of or insulin resistance [31]. In support of a role for LPE as a biomarker for GDM, a non-targeted metabolomic study showed that LPE(16:1) allowed for the classification of subjects as insulin sensitive or insulin resistant [31]. Apart from LPEs, LPIs, in particular, those with long chain-PUFA(18:2, 20:4, 22:6), LPC, phosphatidylcholine (PC) and glycerophosphocholine are also decreased in plasma in the second trimester of GDM [18, 22]. Interestingly, a decrease in various LPC, PC and glycerophosphocoline has been described in T2DM [28, 32]. Furthermore, low levels of LPC(18:2) were proposed to induce glucose-induced insulin secretion from pancreatic cells [6], and to be predictive for dysglycemia and T2DM [6, 7]. Thus, the observed decrease of lysoglycerophospholipids may be associated with glucose intolerance during normal pregnancy, as well as with exacerbated glucose metabolism and cell dysfunction in GDM.

Interestingly, lysoglycerophospholipids acyl moieties are determinant for their effect on glucose/lipid metabolism. Accordingly, in GDM women an increased ratio of saturated/unsaturated acyl chains in LPCs, LPEs and LPIs has been observed [18]. Furthermore, a role of lysoglycerophospholipids with long chain-PUFAs as anti-inflammatory molecules has been suggested [28]. These results, together with the decrease of some lipoxins, potent anti-inflammatory compounds that are considered endogenous anti-diabetic molecules [33], favour the view that an unbalanced proportion of pro-inflammatory *versus* anti-inflammatory molecules is characteristic for GDM development.

A reduction in various sphingomyelins, ceramide-ethanolamines, and sphingosine 1-phosphate has also been described by metabolomics studies not only in T2DM [28, 32] but also in the second [18] and the third trimester of pregnancy in women with GDM [26], being the sphingolipid variations dependent on the metabolic control. According to these findings, the observed decrease in sphingomyelins may be related to the partitioning of palmitate to triacylglycerides in a competitive manner [34], favouring the hypertriglyceridemia observed in GDM (Fig. 2).

Metabolic fingerprinting has also shown that plasmalogens, a group of lipids that may act as serum antioxidants to prevent lipoprotein oxidation [35], are decreased in GDM women [18]. Interestingly, in a previous study from our group [36], we found that, in the second trimester of gestation,

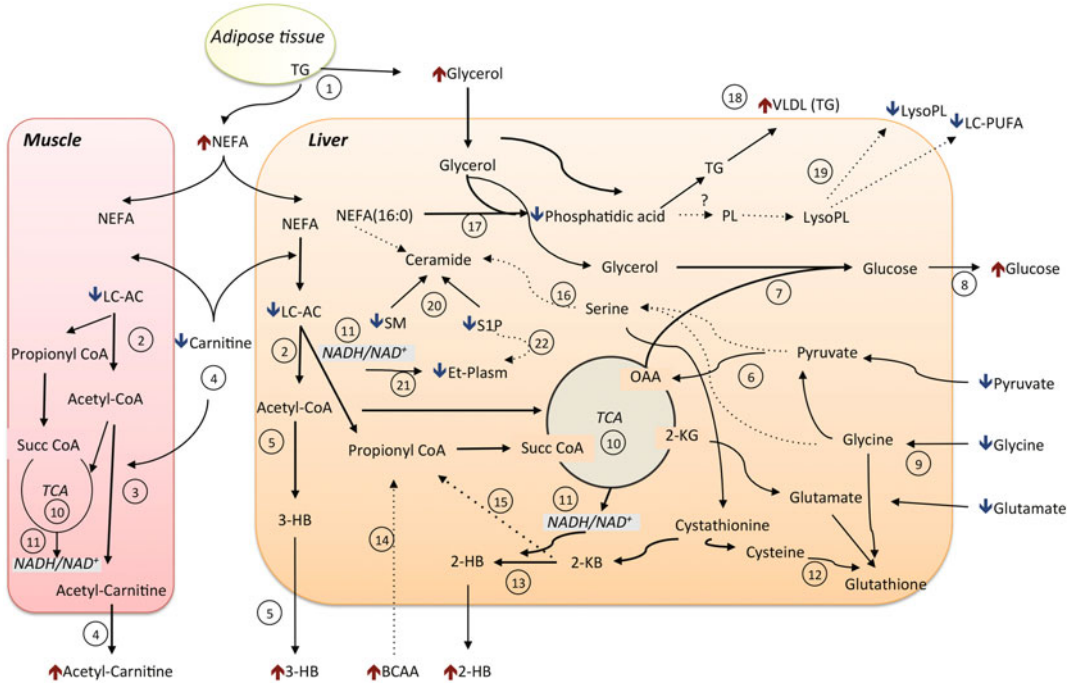


Fig. 2 Model of metabolic alterations in the second trimester of GDM based on metabolomics approaches. Adapted from [18] with results presented in Table 2. GDM is characterized by an increased response to fasting, particularly during early gestation. In this condition, FAs (NEFA) turn into the major energetic substrates, favouring oxidative stress and a mild inflammatory condition. In this scenario, an enhanced lipolysis (*1*) in adipose tissue favours liver and muscle NEFA availability. In both tissues, lipid overload drives an intramitochondrial flux of acyl-CoA for NEFA oxidation, which results in decreased long-chain acylcarnitines (LC-AC) and accumulation of acetyl-CoA, and/or propionyl-CoA (*2*), the end product of metabolism of odd-chain FAs and most of the BCAA. Acetyl-CoA can be converted into acetyl-carnitine (*3*), permitting its mitochondrial efflux that otherwise would inhibit *pyruvate dehydrogenase*. This situation favours depletion of carnitine and, as a result, its decreased excretion into the circulation as well as increased levels of circulating acetyl-carnitine (*4*). In fasting humans, the liver accounts for most of the NEFA oxidation. In this condition, acetyl-CoA can be converted to 3-hydroxybutyrate (3-HB), contributing to the ketonemia found in GDM (*5*), or may favours gluconeogenesis through the activation of the *pyruvate carboxylase* (*6*). Thus, pyruvate and glycerol (*7*) are used preferentially for gluconeogenesis, favouring glucose intolerance in the GDM pregnant women (*8*). Reduced glycine in GDM may also reflect on enhanced gluconeogenesis since this amino acid can be converted to glucose, through pyruvate synthesis, or/and, to glutathione (GSH) (*9*). Enhanced mitochondrial activity, as a consequence of increased NEFA oxidation (*2*) and tricarboxylic acid cycle (TCA) overload (*10*), also increases the NADH + H^+/NAD^+ ratio and oxygen radical production (*11*). To cope with this condition of oxidative stress, glutathione biosynthesis is activated (*12*), which is supported by the observed decreased in glycine and glutamate and the concomitant increase of 2-hydroxybutyrate (2-HB). 2-ketobutyrate (2-KB) is produced through the conversion of cystathionine to cysteine for glutathione biosynthesis (*12*). Next, 2-KB is reduced to 2-HB (*13*), which is favoured by the increased NADH/NAD^+ (*11*). Thus, 2–HB is linked with an increased demand for glutathione biosynthesis and disrupted mitochondrial energy metabolism. Since BCAAs also feed into the TCA, directly or via propionyl-CoA (*14*), the overload of the TCA may lead to the accumulation of AA and 2-ketobutyrate, as this acid is a substrate precursor of both 2-hydroxybutyrate and propionyl-CoA (*15*). The reduced *de novo* sphingolipid synthesis found in GDM, probably as a consequence of serine availability (*16*), favours the flux of palmitate (16:0) towards triacylglycerol (TG) synthesis (*17*), leading to the hypertriglyceridemia observed in GDM women (*18*). In this condition, enhanced triacylglycerol biosynthesis may also cause that phosphatidic acid is not used for the synthesis of glycerophospholipids (PL) (*19*), favouring the observed decrease in lysophospholipids (LysoPL). As a result of the reduced *de novo* sphingolipid synthesis, possibly ceramides are synthesized via sphingomyelin hydrolysis or through the salvage pathway from sphingosine 1-phosphate (S1P) (*20*), which would explain the observed decrease of these lipids. Decreased ethanolamine-plasmalogen (Et-Plasm) levels may be a consequence of their increased utilization as antioxidants (*21*) or of a decreased synthesis from S1P (*18*). Other abbreviations: *OAA* oxaloacetate; 2-KG: 2-ketoglutarate; *Succ CoA* Succinyl-CoA. *Arrows* indicate whether a given metabolite was increased (*red*) or decreased (*blue*) according to the metabolome studies performed up to date (Table 2). *Discontinuous arrows* represent a reduced utilization of the corresponding metabolic route

non-obese women with GDM have already higher plasma concentrations of lipid and protein oxidation products than the control group. Together, these observations point to increased low-grade lipid peroxidation that takes place already at the beginning of GDM.

Fatty Acids and Acyl-Carnitines

An increase in circulating FAs has been associated with insulin resistance in pregnancy, and proposed as a pathogenic factor for risk of preterm delivery [37]. Various metabolomics studies have described elevated levels of FAs, including palmitic, stearic, oleic, linoleic or palmitoleic acid [12, 18, 21]. A study of Chen et al. shows that the absolute concentrations of fasting FAs were elevated in women with GDM both in the second and third trimester of gestation [12]. Furthermore, they showed that many individual FAs were elevated not only in women with GDM but also in non-GDM women with IFG [12, 19]. The observed elevation of circulating free FAs and glycerol [18, 19] is indicative of impaired suppression of lipolysis by insulin, reflecting on the insulin resistance of adipose tissue in the GDM pregnant women. This higher availability of fatty acids in GDM may also favour liver and muscle NEFA availability, which is further supported by the observed increase of by-products of fatty acid oxidation (ketones and tricarboxylic acid cycle–TCA–intermediates) [18, 19, 21].

It is known that carnitine, an essential molecule for FA oxidation in mammals transporting acyl-CoAs, particularly those with long chain, into mitochondria, decreases during gestation [30]. Variations in acyl-carnitines have also been shown during pregnancy. In a metabolomic study it was described a differential regulation of short and long acyl-carnitines during pregnancy. Whereas short-chain acyl-carnitines were elevated in the second trimester and decreased in the last stage of pregnancy, long-chain acyl-carnitines decreased in the second trimester and increased at late gestation [30]. Interestingly, acetyl-carnitine, the main short-chain acylcarnitine, is increased in the second trimester in GDM women, whereas carnitine and long-chain acyl-carnitines are decreased. This variation in acetyl-carnitine in GDM seems to be a common metabolic event of glucose homeostasis alterations, including normal pregnancy [30], IGT [7] and diabetes [38]. These changes suggest that there are different patterns of FA oxidation during GDM that are exacerbated as compared to normal pregnancy. An altered FA oxidation has been linked to insulin resistance and diabetes [39]. Furthermore, various metabolomic studies reported that medium-chain acylcarnitines decrease with IGT [31]. Thus, the observed correlation of acetyl-carnitine and glucose intolerance in GDM tempts us to suggest that, at the beginning of gestation, increased muscle FA oxidation leads to a decrease in long-chain acylcarnitines, together with a concomitant increase of acetyl-CoA (Fig. 2). In fact, in a non-targeted metabolomic study, we observed a decrease of carnitine in the GDM group that seems to be caused by the trapping effect of acetyl-CoA [18]. This is supported by the observation that the ratio of long-chain acylcarnitines/carnitine did not differ between control and diabetic women, whereas the ratio acetyl-carnitine/carnitine was significantly augmented in the GDM women. Furthermore, the observed decrease in carnitine is considered a hallmark of glucose intolerance and insulin resistance [40], and seems to be a metabolic adaptation of normal gestation [30] that it is further exacerbated in those women that develop GDM.

Amino Acids and Derivatives

Previous studies have consistently linked elevated circulating levels of BCAAs with insulin resistance and hyperglycemia and confirmed that these metabolites are significantly increased in obesity and

T2DM [27]. Furthermore, metabolomic analysis has identified isoleucine, leucine and valine as relevant diabetes risk markers [41].

Changes in plasma concentration of AAs have also been found to be altered in GDM, in particular, BCAAs [19–23, 25, 26] and aromatic AAs [18, 19, 24]. Although there are some discrepancies between different studies, those including a higher number of patients have reported an elevation in circulating BCAAs in GDM, even in the first trimester before the diagnosis of the disease [20, 21]. Similarly, some previous non-metabolomic studies have also demonstrated higher levels of BCAAs in GDM [42]. The elevation in BCAA may be related to a reduced amino acid transport and/or clearance [43, 44] such as described for other situations associated with insulin resistance.

Besides BCAA and aromatic AAs, we and other groups have reported on the significant reduction of glycine in plasma [18, 25] and amniotic fluid [13] in the second trimester of gestation in GDM women. Interestingly, various metabolomics studies have also found a decrease of glycine in patients with impaired glucose tolerance, T2DM, obesity and impaired insulin sensitivity [31, 45]. Furthermore, results obtained in various prospective studies, point to decreased glycine as an independent predictor of T2DM [28] and IGT [7]. The reduced levels of glycine in GDM may reflect on enhanced gluconeogenesis, glutathione synthesis [46] or both (Fig. 2). The role of glycine as an indicator of activated gluconeogenesis is further support by decreased pyruvate during fasting in GDM [18, 25]. In fasting conditions, pyruvate is used preferentially for gluconeogenesis rather than for oxidation upon conversion to acetyl-CoA. Thus, FAs turn into the predominant substrate for energy production. A switch to FA oxidation is further supported by increased levels of 3-hydroxybutyrate under fasting conditions in GDM women [18] and in pregnant women with impaired fasting glucose [19]. In this scenario, the augmented NEFA oxidation to acetyl-CoA, which feeds into the TCA, leads to an excess of reducing equivalents (NADH). Since BCAAs also feed into the TCA, directly or via propionyl-CoA, the overload of the TCA may lead to the accumulation of AAs, such as alanine [19–21] and 2-ketobutyrate [31], a substrate precursor of 2-hydroxybutyrate and propionyl-CoA. In fact, plasma 2-hydroxybutyrate levels have been reported to be higher in GDM than in control subjects [18, 19]. 2-hydroxybutyrate is elevated in human and animal models of T2DM [47] and has been proposed as an independent and early predictor of glucose intolerance in humans [6, 31]. As detailed in Fig. 2, the interpretation that a redox imbalance may contribute to elevated 2-hydroxybutyrate is consistent with the finding that FA oxidation is increased in GDM.

In normal pregnancies, most maternal AAs were reported to decrease during early gestation, reflecting on a metabolic adaptation that occurs upon demand by the foetus [48]. However, pregnancies that develop intrauterine growth retardation at a later stage show a lack of these adaptations [49]. Since changes in plasma concentration of AAs may play an important role in appropriate foetal growth, the lack of amino acid adaptation during pregnancy in GDM may contribute to the alterations in foetal development associated with this disease.

Guideline Recommendations: Samples for Metabolomics Analysis

The metabolome is dynamic, and metabolic flux can operate with a time frame of seconds depending on the metabolic reaction being studied. As a consequence, quantitative metabolic profile is changing during sample collection and could substantially vary if appropriate conditions are not considered [1, 50]. Therefore, sample collection is one of the most important aspects of the metabolomics experimental workflow. Rapid inhibition of enzymatic processes is required, and generally that is achieved by freezing in liquid nitrogen after sample harvesting (especially in the case of tissues) and subsequent storage at −80 °C. The choice of the specimen is an important issue, and should be based on the objectives of the study. In applications focused on development of biomarkers, biofluids (plasma, serum or urine) are the most common. Blood collection is easily accessible, and complications due to

sampling procedure are rare. Both serum and plasma can provide complex data of both physiological and pathophysiological conditions at a given time [51]. However, collection of plasma is more reproducible as, in serum collection blood clotting can be a source of variability. Many analyses have shown that the metabolome of serum and plasma are similar, therefore the choice of one or other biofluid will have a minimal impact on most studies [52, 53]. Meanwhile, mechanistic studies are usually based on cell cultures or tissues where changes are directly being produced. Consistent sample handling, as well as prompt storage of samples, minimize the variability in the subsequent analysis, and ensure the quality of output metabolomics data.

General Remarks

- Variables to consider: collection technique, time of sampling, gender, age, diet, hydration, fasting, exercise/activity.
- Collection, storage and preparation of samples should be standardized to assure the reproducibility.
- Plasma obtained with different anticoagulants (e.g. EDTA, heparin) and analyzing plasma and serum samples in the same experiment are absolutely forbidden.
- Sample processing should be as quick as possible.
- Samples should be stored at −80 °C.
- Minimize freeze-thawing cycle to avoid degradation or formation of new metabolites.
- Hemolytic samples should be excluded.

Conclusions

Despite several recommendations, there is no consensus approach to GDM diagnosis. Thus, the availability of metabolites (or metabolic patterns) that predict GDM would be a major advance.

Metabolomic studies have the potential to determine a unique and disease-specific metabolite pattern or "fingerprint" which allows for deciphering biological processes and may be predictive of the disease, even before its onset. Thus, although much work remains to be done, the evidence of metabolomics benefitting health care makes its general clinical application inevitable, including the case of GDM.

As yet, the available metabolomics studies demonstrate a broad scale of metabolic differences associated with GDM, including metabolic imbalances such as low-grade inflammation and altered redox-balance. These studies provide insights into the underlying mechanisms and metabolic consequences of the disease and pinpoint a number of metabolites that hold the promise to be useful as prognostic and/or diagnostic biomarkers to predict the onset of GDM and/or the diabetic complications in GDM women after delivery. Future population-based studies, including targeted validation in different cohorts, will allow to validate these potential biomarkers, and to establish their clinical relevance.

References

1. Dunn WB, Broadhurst DI, et al. Systems level studies of mammalian metabolomes: the roles of mass spectrometry and nuclear magnetic resonance spectroscopy. Chem Soc Rev. 2011;40:387–426.

2. Patti GJ, Yanes O, et al. Innovation: Metabolomics: the apogee of the omics trilogy. Nat Rev Mol Cell Biol. 2012;13:263–9.
3. Alonso A, Marsal S, et al. Analytical methods in untargeted metabolomics: state of the art in 2015. Front Bioeng Biotechnol. 2015;3:23.
4. Gika HG, Wilson ID, et al. LC-MS-based holistic metabolic profiling. Problems, limitations, advantages, and future perspectives. J Chromatogr B Analyt Technol Biomed Life Sci. 2014;966:1–6.
5. Ellis DI, Dunn WB, et al. Metabolic fingerprinting as a diagnostic tool. Pharmacogenomics. 2007;8:1243–66.
6. Ferrannini E, Natali A, et al. Early metabolic markers of the development of dysglycemia and type 2 diabetes and their physiological significance. Diabetes. 2013;62:1730–7.
7. Wang-Sattler R, Yu Z, et al. Novel biomarkers for pre-diabetes identified by metabolomics. Mol Syst Biol. 2012;8:615.
8. Klein MS, Shearer J. Metabolomics and type 2 diabetes: translating basic research into clinical application. J Diab Res. 2016;2016:3898502.
9. Varvel SA, Voros S, et al. Comprehensive biomarker testing of glycemia, insulin resistance, and beta cell function has greater sensitivity to detect diabetes risk than fasting glucose and HbA1c and is associated with improved glycemic control in clinical practice. J Cardiovasc Transl Res. 2014;7:597–606.
10. Sachse D, Sletner L, et al. Metabolic changes in urine during and after pregnancy in a large, multiethnic population-based cohort study of gestational diabetes. PLoS One. 2012;7:e52399.
11. Bock JL. Metabolic profiling of amniotic fluid by proton nuclear magnetic resonance spectroscopy: correlation with fetal maturation and other clinical variables. Clin Chem. 1994;40:56–61.
12. Chen X, Scholl TO, et al. Differences in maternal circulating fatty acid composition and dietary fat intake in women with gestational diabetes mellitus or mild gestational hyperglycemia. Diab Care. 2010;33:2049–54.
13. Graca G, Duarte IF, et al. Impact of prenatal disorders on the metabolic profile of second trimester amniotic fluid: a nuclear magnetic resonance metabonomic study. J Proteome Res. 2010;9:6016–24.
14. Diaz SO, Pinto J, et al. Metabolic biomarkers of prenatal disorders: an exploratory NMR metabonomics study of second trimester maternal urine and blood plasma. J Proteome Res. 2011;10:3732–42.
15. Graca G, Goodfellow BJ, et al. UPLC-MS metabolic profiling of second trimester amniotic fluid and maternal urine and comparison with NMR spectral profiling for the identification of pregnancy disorder biomarkers. Mol BioSyst. 2012;8:1243–54.
16. Diaz SO, Barros AS, et al. Second trimester maternal urine for the diagnosis of trisomy 21 and prediction of poor pregnancy outcomes. J Proteome Res. 2013;12:2946–57.
17. de Seymour JV, Conlon CA, et al. Early pregnancy metabolite profiling discovers a potential biomarker for the subsequent development of gestational diabetes mellitus. Acta Diabetol. 2014;51:887–90.
18. Dudzik D, Zorawski M, et al. Metabolic fingerprint of gestational diabetes mellitus. J Proteomics. 2014;103:57–71.
19. Scholtens DM, Muehlbauer MJ, et al. Metabolomics reveals broad-scale metabolic perturbations in hyperglycemic mothers during pregnancy. Diab Care. 2014;37:158–66.
20. Bentley-Lewis R, Huynh J, et al. Metabolomic profiling in the prediction of gestational diabetes mellitus. Diabetologia. 2015;58:1329–32.
21. Enquobahrie DA, Denis M, et al. Maternal early pregnancy serum metabolites and risk of gestational diabetes mellitus. J Clin Endocrinol Metab. 2015;100:4348–56.
22. Lehmann R, Friedrich T, et al. Metabolic profiles during an oral glucose tolerance test in pregnant women with and without gestational diabetes. Exp Clin Endocrinol Diab. 2015;123:483–38.
23. Hajduk J, Klupczynska A, et al. A combined metabolomic and proteomic analysis of gestational diabetes mellitus. Int J Mol Sci. 2015;16:30034–45.
24. Lorenzo MP, Dudzik D, et al. Optimization and validation of a chiral GC-MS method for the determination of free D-amino acids ratio in human urine: application to a gestational diabetes mellitus study. J Pharm Biomed Anal. 2015;107:480–7.
25. Pinto J, Almeida LM, et al. Prediction of gestational diabetes through NMR metabolomics of maternal blood. J Proteome Res. 2015;14:2696–706.
26. Liu T, Li J, et al. Comprehensive analysis of serum metabolites in gestational diabetes mellitus by UPLC/Q-TOF-MS. Anal Bioanal Chem. 2016;408:1125–35.
27. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. Nat Rev Endocrinol. 2014;10:723–36.
28. Floegel A, Stefan N, et al. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. Diabetes. 2013;62:639–48.
29. Hung ND, Kim MR, et al. 2-Polyunsaturated acyl lysophosphatidylethanolamine attenuates inflammatory response in zymosan A-induced peritonitis in mice. Lipids. 2011;46:893–906.
30. Luan H, Meng N, et al. Pregnancy-induced metabolic phenotype variations in maternal plasma. J Proteome Res. 2014;13:1527–36.

31. Gall WE, Beebe K, et al. Alpha-hydroxybutyrate is an early biomarker of insulin resistance and glucose intolerance in a nondiabetic population. PLoS One. 2010;5:e10883.
32. Suhre K, Meisinger C, et al. Metabolic footprint of diabetes: a multiplatform metabolomics study in an epidemiological setting. PLoS ONE. 2010;5:e13953.
33. Das UN. Arachidonic acid and lipoxin A4 as possible endogenous anti-diabetic molecules. Prostaglandins Leukot Essent Fatty Acids. 2013;88:201–10.
34. Watson ML, Coghlan M, et al. Modulating serine palmitoyl transferase (SPT) expression and activity unveils a crucial role in lipid-induced insulin resistance in rat skeletal muscle cells. Biochem J. 2009;417:791–801.
35. Wallner S, Schmitz G. Plasmalogens the neglected regulatory and scavenging lipid species. Chem Phys Lipids. 2011;164:573–89.
36. Ramos Alvarez MP, Viana M, et al. Gestational diabetes and obesity: role of oxidative stress and inflammation. FEBS Lett. 2012;279.
37. Chen X, Scholl TO. Association of elevated free fatty acids during late pregnancy with preterm delivery. Obstet Gynecol. 2008;112:297–303.
38. Adams SH, Hoppel CL, et al. Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid β-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic african-american women. J Nutr. 2009;139:1073–81.
39. Schooneman MG, Vaz FM, et al. Acylcarnitines: reflecting or inflicting insulin resistance? Diabetes. 2013;62:1–8.
40. Poorabbas A, Fallah F, et al. Determination of free L-carnitine levels in type II diabetic women with and without complications. Eur J Clin Nutr. 2007;61:892–5.
41. Wang TJ, Larson MG, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011;17:448–53.
42. Metzger BE, Phelps RL, et al. Effects of gestational diabetes on diurnal profiles of plasma glucose, lipids, and individual amino acids. Diab Care. 1980;3:402–9.
43. Bonadonna RC, Saccomani MP, et al. Effect of insulin on system A amino acid transport in human skeletal muscle. J Clin Invest. 1993;91:514–21.
44. Fiehn O, Garvey WT, et al. Plasma metabolomic profiles reflective of glucose homeostasis in non-diabetic and type 2 diabetic obese african-american women. PLoS One. 2010;5:e15234.
45. Wurtz P, Makinen VP, et al. Metabolic signatures of insulin resistance in 7098 young adults. Diabetes. 2012;61:1372–80.
46. Sekhar RV, McKay SV, et al. Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diab Care. 2011;34:162–7.
47. Salek RM, Maguire ML, et al. A metabolomic comparison of urinary changes in type 2 diabetes in mouse, rat, and human. Physiol Genomics. 2007;29:99–108.
48. Pinto J, Barros AS, et al. Following healthy pregnancy by NMR metabolomics of plasma and correlation to urine. J Proteome Res. 2015;14:1263–74.
49. Di Giulio AM, Carelli S, et al. Plasma amino acid concentrations throughout normal pregnancy and early stages of intrauterine growth restricted pregnancy. J Matern Fetal Neonatal Med. 2004;15:356–62.
50. Dunn WB, Broadhurst D, et al. Procedures for large-scale metabolic profiling of serum and plasma using gas chromatography and liquid chromatography coupled to mass spectrometry. Nat Protoc. 2011;6:1060–83.
51. Walsh MC, Brennan L, et al. Effect of acute dietary standardization on the urinary, plasma, and salivary metabolomic profiles of healthy humans. Am J Clin Nutr. 2006;84:531–9.
52. Denery JR, Nunes AA, et al. Characterization of differences between blood sample matrices in untargeted metabolomics. Anal Chem. 2011;83:1040–7.
53. Liu L, Aa J, et al. Differences in metabolite profile between blood plasma and serum. Anal Biochem. 2010;406:105–12.
54. Kell DB, Brown M, et al. Metabolic footprinting and systems biology: the medium is the message. Nat Rev Microbiol. 2005;3:557–65.
55. Nicholson JK, Lindon JC, et al. 'Metabonomics': understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. Xenobiotica. 1999;29:1181–9.
56. Fiehn O. Metabolomics–the link between genotypes and phenotypes. Plant Mol Biol. 2002;48:155–71.
57. Oliver SG, Winson MK, et al. Systematic functional analysis of the yeast genome. Trends Biotechnol. 1998;16:373–8.
58. Hollywood K, Brison DR, et al. Metabolomics: current technologies and future trends. Proteomics. 2006;6: 4716–23.
59. Dunn WB, Ellis DI. Metabolomics: current analytical platforms and methodologies. Trends Anal Chem. 2005;24:285–94.

Chapter 11
Genetic and Epidemiological Indications for Adiponectin Gene Dysregulation in Gestational Diabetes Mellitus

Olga Beltcheva, Maria Boyadzhieva, Vanio Mitev and Radka Kaneva

Key Points

Adiponectin is a member of the growing family of adipokines, biologically active molecules produced and secreted by the adipose tissue. It is a 244 amino acid long protein, coded for by the *ADIPOQ* gene, which is synthesized exclusively in the adipocytes. The goal of the current chapter is to discuss:

- the role of adiponectin for carbohydrate and lipid metabolism. Although its biological function is not completely understood, there is sufficient evidence that it stimulates fatty acid oxidation, inhibits gluconeogenesis and increases insulin sensitivity. Adiponectin's presence in plasma and its role as regulator of energy homeostasis makes it a perfect candidate for diagnostic marker of various metabolic disorders. It has also been viewed as a potential therapeutic target. All this explains the great research interest in the structure, regulation, and metabolic effect of adiponectin.
- adiponectin's influence on metabolism during pregnancy and its involvement in the etiology of gestational diabetes mellitus. Pregnancy is a physiological stage associated with transient insulin resistance resulting from significant changes in maternal metabolism, which allow it to accommodate the needs of the growing fetus. It is believed that among the factors contributing to this metabolic adjustment is the progressive decline of adiponectin concentration in plasma during gestation. Dysregulation of these processes may lead to complications such as gestational diabetes mellitus (GDM). The applicability of adiponectin plasma levels as stratification marker for identification of women at risk for GDM is addressed.
- the current knowledge of the regulation of adiponectin gene. The activity of *ADIPOQ* depends on the interaction between gene-specific DNA *cis* regulatory elements and *trans* acting factors influencing the differentiation and function of adipocytes. For example, we know that the gene is turned on by PPARγ/RXR and C/EBP, and repressed by TNF-α through their interaction with a

O. Beltcheva (✉) · R. Kaneva
Molecular Medicine Center, Department of Medical Chemistry and Biochemistry,
Medical University of Sofia, SBALAG Maichin dom, fl. 14, 2 "Zdrave" str, Sofia, Bulgaria
e-mail: beltcheva@mmcbg.org; oblatche@gmail.com

R. Kaneva
e-mail: kaneva@mmcbg.org

M. Boyadzhieva
Clinical Center of Endocrinology, USBALE "Acad. Iv. Pentchev", Medical University of Sofia,
2 "Zdrave" str, Sofia, Bulgaria
e-mail: mariq_b@yahoo.com

V. Mitev
Department of Medical Chemistry and Biochemistry, Medical University of Sofia,
15 "Acad. E. I. Geshov" Boul, Sofia, Bulgaria
e-mail: mitev@medfac.acad.bg

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_11

number of upstream binding sites. A summary of our current understanding of the interactions governing *ADIPOQ* regulation is presented. Despite the accumulation of substantial knowledge about the general mechanisms for *ADIPOQ* regulation, the fine tuning of its transcription under normal physiological changes such as pregnancy or its dysregulation in case of pathology is still not well understood.

- the effect of a common genetic polymorphism, rs266729, on *ADIPOQ* expression and the contribution of the variant allele to the individual risk for gestational diabetes. The variant is located upstream of the adiponectin gene and has been shown to affect the binding of nuclear factors to specific DNA sequences. A genetic association study carried out by our research team indicated a possible role of rs266729 for the development of GDM. A hypothesis of the putative molecular mechanism underlying this association is presented. Directions for future research of the effect of rs266729 on health and disease are proposed.

Keywords Adiponectin · ADIPOQ · GDM · Rs266729 · Genetic polymorphism

Abbreviations

GDM	Gestational diabetes mellitus
ADIPOQ	Adiponectin gene
TNF-α	Tumor necrosis factor α
PAI-1	Plasminogen activator inhibitor-1
CRP	C-reactive peptide
SREBP	Sterol regulatory element binding proteins
C/EBPα and C/EBPβ	CCAAT/enhancer binding protein α and β
PPARγ	Peroxisome proliferator-activated receptor-gamma
RXR	Retinoid X receptor
LRH-1	Liver receptor homolog-1
HOMA	Homeostasis model assessment
GCKR	Glucokinase regulatory protein
INS	Insulin gene
GLUT	Glucose transporter
AMPK	AMP-activated kinase
MAPK	Mitogen-activated protein kinase
OR	Odds ratio

Introduction

The adipose tissue, traditionally viewed as a storage place for lipids and an insulator, is now understood to play essential role in many physiological processes related to metabolism, appetite, growth, and reproduction. The ability of adipocytes to synthesize and secrete various biologically active molecules, hormones, and cytokines, have allowed many authors to classify this tissue as an endocrine organ. Collectively known as adipocytokines (adipokines for short), these molecules are involved in the regulation of metabolism, inflammation, blood clothing, etc. Some of them are characteristic of adipocytes, such as adiponectin, leptin, resistin, and vaspin, while others are produced by a larger number of cell and tissue types—interleukin-6, tumor necrosis factor α (TNF-α), plasminogen activator inhibitor-1 (PAI-1), and the renin-angiotensin system components. As a rule,

an increased adipocyte number and size is associated with increased production of adipokines, although an inverse relationship is characteristic for adiponectin and omentin 1 [1].

The adipokines' role for regulation of the carbohydrate and lipid metabolism, appetite, blood pressure, clotting, and inflammation, has attracted a lot of attention during the last decade. Attempts have bene made to clarify their putative involvement in the cardiovascular disorders, obesity, metabolic syndrome, diabetes, gestational diabetes mellitus (GDM), etc. Best understood in respect to GDM is the role of adiponectin and leptin. The contribution of the other adipose tissue-specific cytokines to the pathology of this condition is still unclear because of the limited number of studies or the contradictory results published by various groups [2–4].

A brief overview of our current knowledge of the adipokines' tissue and cell specificity as well as their major functions is presented in Table 11.1. The present chapter will focus on one of their representatives, adiponectin.

Adiponectin

Adiponectin is a 244 amino acid long protein, product of the *ADIPOQ* gene, with collagen like and complement 1q like domains. It is synthesized and secreted exclusively by adipocytes, and acts as a regulator of carbohydrate and lipid metabolism. More specifically, it stimulates fatty acid oxidation, inhibits gluconeogenesis and increases insulin sensitivity of various tissues such as muscle and liver [5]. Adiponectin has anti-inflammatory function and is known to impede arterial plaque formation. It inhibits TNF-alpha expression in a number of tissues including liver and macrophages, and counters its pro-inflammatory effects. In addition, it stimulates energy expenditure, an effect mediated by the central nervous system. Given its metabolic role, it is not surprising that the development of adiponectin receptor agonists is considered when discussing more advanced forms of glucose lowering treatments [6].

Adiponectin is found in different multimeric forms—low-molecular weight (LMW) homo-trimers, medium molecular weight (MMW) homo-hexameres, and high-molecular weight (HMW) multimeres containing 12-18 polypeptides. The oligomerization depends on the formation of disulfide bonds linking the amino-terminal cysteines regulated by the disulfide-bond A oxidoreductase-like protein (DsbA-L) [7]. Of note, the induction of adiponectin synthesis and secretion by antidiabetic drug rosiglitazone appears to be mediated by DsbA-L. Apart from their size, LMW, MMW, and HMW adiponectin isoforms also differ in their degree of glycosylation, which may affect their synthesis and/or secretion. The size and relative ratios of the adiponectin oligomers seem to affect its metabolic role [8]. For example, the HMW form is known to have an increased half-life and insulin-sensitizing effect. What is more, adiponectin's secretion by the adipocytes appears to depend on its oligomerization since mutations affecting the normal formation of the disulfide bridges required for the multimers' assembly results in inhibition of its signaling effects in hepatocytes [9].

An additional, shorter form of adiponectin, designated globular adiponectin, has also been found in the circulation. It appears to be a product of proteolytic cleavage of the full-length protein. In some tissues both variants have similar effects, but for placenta differences have been observed [10, 11]. At present not much is known about the function of the short globular adiponectin, which is present in much lower concentrations in plasma.

Adiponectin exerts its effects via two receptors–AdipoR1 and AdipoR2, which are expressed by a large number of cells [12, 13]. While AdipoR1 is found ubiquitously and binds the globular adiponectin with higher affinity compared to the full-length protein, AdipoR2 is specific for liver and exhibits no preference for either isoform, binding both with intermediate affinity. The crystal structures of both AdipoR1 and AdipoR2 have been solved recently [12]. The adiponectin receptors appear to be very similar to G-coupled receptors in that they possess a seven membrane spanning domain but unlike

Table 11.1 A list of adipocytokines produced by adipocytes

Adipokine	Expression	Function
Leptin	Mainly produced by adipocytes, expressed also in skeletal muscle, salivary glands, placenta, etc.	Major regulator of energy balance. Binding to receptors in the hypothalamus leads to decrease in food intake and increase in energy expenditure. In the periphery, increases basal metabolism, regulates pancreatic beta-cell function and insulin secretion, has pro-angiogenic properties, etc
Adiponectin	Exclusively by adipocytes	Plays role in the regulation of fat metabolism and insulin sensitivity by stimulating glucose uptake and fatty acid oxidation. Possesses anti-diabetic, anti-atherogenic, and anti-inflammatory activities
Resistin	Mainly in adipose tissue, produced by peripheral blood mononuclear cells. Expressed also in placenta	Suppresses insulin's ability to stimulate glucose uptake by adipose cells
FABP 4 (fatty acid binding protein)	Adipocytes, macrophages, and placenta	Delivers long-chain fatty acids and retinoic acid to their cognate receptors in the nucleus
IL-6 (interleukin 6)	Expressed in immune cells and bone marrow, liver, intestine, skeletal and smooth muscle, etc. In adipose tissue it is produced by adipocytes, stromal vasculature, and immune cells. During pregnancy synthesized in placenta	Cytokine with essential role in acute phase response, lymphocyte, and monocyte differentiation. Regulation of hematopoiesis. Myokine. Involved in bone resorption. Has central (CNS) and peripheral-mediated effect on glucose metabolism and insulin sensitivity
Visfatin	Highest level in liver, muscle and bone marrow. Observed also in visceral adipose tissue, heart, placenta, etc.	Rate limiting enzyme in the NAD biosynthesis pathway. Its secretory form has anti-diabetic properties due to its ability to bind insulin receptor and stimulate glucose uptake
Omentin 1 (intelectin 1)	Highly expressed in the vasculature of omental adipose tissue, almost undetectable in subcutaneous fat. Expression observed also in skeletal muscle, heart, pancreas, colon, etc.	Enhances insulin-stimulated glucose uptake in adipocytes. Alters AKT phosphorylation in response to insulin signaling
Vaspin (serpin A12)	Adipocytes in visceral adipose tissue	Modulates insulin action by inhibiting its protease(s) in white adipose tissue. Has insulin-sensitizing effect
RBP4 (retinol binding protein 4)	Liver and adipocytes	Delivers retinol from the liver stores to the peripheral tissues. Stimulates gluconeogenesis in liver and inhibits glucose uptake in muscle
Perilipin-1	Adipocytes and placenta	Modulator of adipocyte lipid metabolism. Coats lipid storage droplets to protect them from breakdown by hormone-sensitive lipase (HSL). Modulates lipolysis and triglyceride levels

(continued)

Table 11.1 (continued)

Adipokine	Expression	Function
Apelin	Expressed in central nervous system and a large number of peripheral tissue and cell types including endothelium, adipocytes, and placenta	Ligand of the G-protein-coupled receptor APJ, which participates in the regulation of the normal physiological functions in gastrointestinal tract, cardiovascular functions, and central nervous system. Involved in endothelium-mediated vasodilation
PAI-1 (endothelial plasminogen activator inhibitor; serpine 1)	Produced mainly by the endothelium. Expressed in adipocytes	Serine protease inhibitor involved in regulation of fibrinolysis. Acts as 'bait' for tissue plasminogen activator, urokinase, protein C, and matriptase-3/TMPRSS7
Adipsin (complement factor D)	Adipocytes, monocytes, and macrophages	A serine protease involved in complement activation. May have role in stimulation of triglyceride synthesis in adipocytes
HSL (hormone-sensitive lipase)	Adipocytes and steroidogenic tissue	In adipose tissue and heart its short form hydrolyzes stored triglycerides to free fatty acids. In steroidogenic tissues, the long variant converts cholesteryl esters to free cholesterol for steroid hormone production
CETP (cholesterol ester transfer protein)	Expressed in liver. In adipose tissue synthesized in adipocytes	Enzyme involved the exchange of cholesteryl ester from HDL to VLDL, and the equimolar transport of triglyceride from VLDL to HDL
LPL	Adipocytes, skeletal muscle cells, liver, kidney, etc.	Enzyme involved in the hydrolysis of triglycerides of circulating chylomicrons and very low density lipoproteins (VLDL). It is excreted and attaches to the endothelium through binding to heparin sulfate proteogylcans
ASP (acylation stimulating protein)	Exclusively in adypocytes	An adipogenic hormone that stimulates triglyceride synthesis and glucose transport in adipocytes, regulating fat storage, and playing a role in postprandial TG clearance
Renin-angiotensin system components	Adipocytes, endothelium, renal epithelial, and juxtaglomerular cells, liver, etc.	A hormonal system involved in the regulation of blood volume and systemic vascular resistance
TNF-α	Mainly by macrophages, but expression is observed in other immune cells, such as eosinophils, neutrophils, monocytes, etc. In adipose tissue it is synthesized in adipocytes and stromal vasculature. During pregnancy produced in placenta	Involved in inflammation, immune response, and apoptosis
CRP (C-reactive protein)	Exclusively by liver, also in lymphocytes and adipocytes	Involved in host defense. Produced and excreted in plasma during the acute phase of the immune reaction to tissue damage

(continued)

Table 11.1 (continued)

Adipokine	Expression	Function
MCP-1 (monocyte chemotactic protein-1)	Synthesized by macrophages, endothelium, smooth muscle cells, and adipocytes	Its expression and secretion is induced by insulin. Stimulates adipocyte differentiation. Facilitates the migration of monocytes and macrophages into sites of inflammation. Secreted MCP-1 may attenuate insulin signaling and glucose uptake in skeletal muscle. Overexpressed in obesity
ICAM-1	Specific for endothelial cells and cells of the immune system, also adipocytes	*ICAM-1* gene expression is induced in adipose tissue in response to high fat diet. Facilitates migration of monocytes and macrophages into sites of inflammation

Function descriptions are based on the information provided in Uniprot, OMIM, and Ensembl

them are characterized with reverse orientation of the termini - extracellular C and intracellular N-terminus. Based on the crystal structure, the transmembrane domain is understood to form a cavity containing zinc ion coordinated by three conserved histidines. This zinc-binding structure is predicted to play role in AMPK phosphorylation and activation of uncoupling protein 2. In vitro studies suggest APPL1 as a possible intracellular partner in signal mediation of both receptors [14].

Binding of adiponectin to its receptors activates a number of signaling pathways mediated by AMPK, p38 MAPK, PPARα, and Rab5. The interaction ultimately results in increased fatty acid oxidation, glucose transporter mobilization, and glucose uptake along with inhibition of gluconeogenesis. A schematic presentation summarizing our current understanding of the adiponectin signaling is shown in Fig. 11.1.

As discussed earlier, the concentration of adiponectin diminishes with the increase of the adipose deposits. Low levels of this adipokine in plasma are associated with insulin resistance, obesity, metabolic syndrome, type 2 diabetes, and ischemic heart disease.

Adiponectin in Normal and GDM Pregnancy

During pregnancy maternal metabolism undergoes significant changes in order to accommodate the needs of the growing fetus. This period is associated with transient insulin resistance as well as increase in the adipose deposits. Changes in the normal physiological processes governing this adjustment may lead to complications such as gestational diabetes mellitus (GDM). In GDM, the β-cells cannot compensate for the increased insulin resistance associated with the pregnancy. As a result, maternal glucose intolerance develops which is clinically diagnosed in the second trimester. With its incidence amongst future mothers of 2–10% in Europe and USA as well as the impact of the associated complications for mother and child, GDM has been a subject of considerable research interest during the last decades. Particular attention has been paid to the role of adipokines for this pathological condition because of their involvement in the maintenance of energy homeostasis. During gestation, plasma concentration of adiponectin progressively declines reaching a minimum during the second trimester. Of note, ethnic variations of its levels during normal gestation have been observed [15].

Surprisingly, some authors notice that the decline of adiponectin in maternal serum with the advance of pregnancy is accompanied by significant increase of the concentration in umbilical cord [16, 17]. This has led some researchers to speculate that in gestation adiponectin is produced also in fetal tissues. In confirmation of this hypothesis Chen et al. report *ADIPOQ* expression in syncytiotrophoblast along with increased expression of adiponectin receptors in placenta [18].

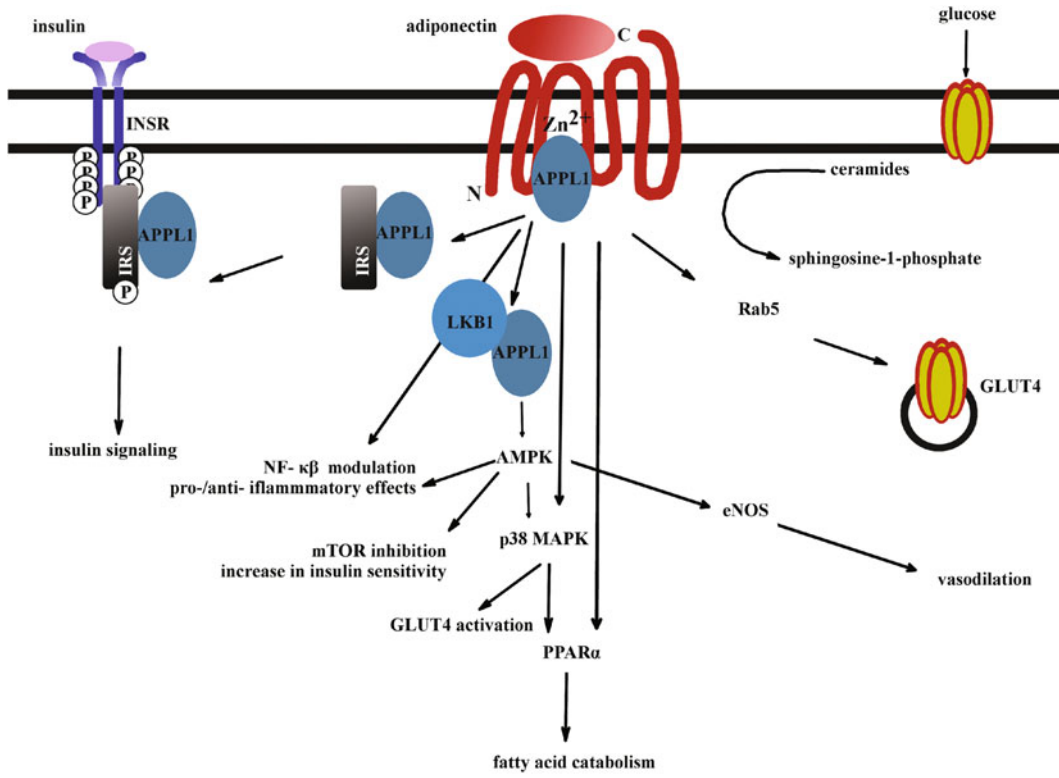


Fig. 11.1 Adiponectin signal transduction. Adiponectin signaling is mediated by its receptors (AdipoR1 and R2) and the APPL1 adaptor molecule. It triggers GLUT4 glucose transporter translocation via direct interaction with the small GTPase Rab5; activates AMP kinase pathway via its collaboration with LKB1 kinase, leading to increased insulin sensitivity (by means of mTOR inhibition), fatty acid catabolism (with the help of p38 MAPK and PPARα), glucose uptake (through p38 MAPK), and vasodilation (through eNOS); modulates the inflammatory response of the cell by direct or AMPK-mediated regulation of NF-κβ; decreases the ceramide concentration by the receptor's ceramidase activity, thus reducing their insulin resistance effect. In addition, APPL1 is responsible for the cross-talk between adiponectin and insulin receptors through its interaction with insulin receptor substrates 1 and 2 (IRS). The figure presents a general and by no means comprehensive picture of adiponectin signaling. Interactions and effects may differ depending on the receptor (AdipoR1 or R2) or cell type as well as metabolic states

At the same time, other researchers have failed to detect *ADIPOQ* expression in placenta explaining the controversial results with contamination with material from the maternal circulation or cell culture serums [11, 19–21]. Thus, the question of the origin of adiponectin during pregnancy is still open to debate.

While adiponectin increases the insulin sensitivity of various maternal tissues, its effect on the fetus, more specifically, the placenta (for adiponectin does not readily cross this barrier), appears to be different [22]. In vitro experiments have demonstrated that it inhibits insulin signaling and insulin-stimulated amino acid transport in primary human trophoblast cell lines [23]. The effect is achieved via activation of peroxisome proliferator-activated receptor-α (PPARα), followed by an increase of ceramide production and attenuation of insulin signaling. This cellular response to adiponectin is in contrast to that described for muscle and liver cells (see Fig. 1). Such placenta-specific effects of maternal adiponectin have been observed also in in vivo experiments with mice [24]. These findings support a model of mother–fetus interactions where maternal signals modulate insulin signaling in the placenta and consequently, the availability of nutrients for the fetus.

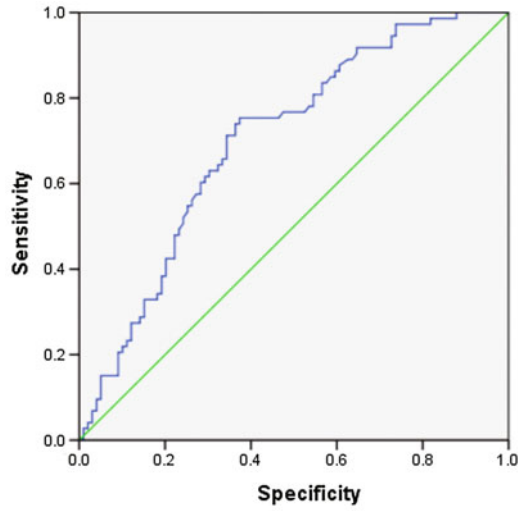


Fig. 11.2 Receiver-operating characteristic curve demonstrating the plot between sensitivity and specificity for adiponectin levels during pregnancy as a predictor for gestational diabetes status. Using a lower cutoff value of 8.2 μg/ml, maternal serum adiponectin could exclude GDM with a sensitivity of 83.6% and a specificity of 56.6% (area under the curve (AUC) = 0.702, SE = 0.04, 95% CI 0.625–0.780, $p < 0.0001$)

The normal physiological decline of adiponectin in pregnancy is even more exaggerated in women with GDM. In human subjects, low circulating levels of the HMW adiponectin are consistently associated with increased risk for GDM independent of the maternal body mass index [2, 25, 26]. A large number of independent researchers have studied the fluctuation of circulating adiponectin in gestation finding significantly lower levels of this adipokine in GDM pregnancy. A study carried out by members of our team compared the levels of circulating adiponectin in GDM women and controls both during gestation and postpartum finding that it can be used as a predictor for the condition with sensitivity of 83.6% and a specificity of 56.6% for cutoff value of 8.2 μg/ml [27]. A ROC curve illustrating this analysis can be seen bellow (see Fig. 11.2).

A meta-analysis summarizing the results of 11 investigations carried out between 2004 and 2014 confirmed that adiponectin levels in maternal plasma may in fact be used to evaluate the risk of developing GDM later on during pregnancy [28]. In addition, low levels of adiponectin appear to be correlated with increased birth weight in both normal and GDM pregnancies even after accounting for paternal body mass index before conception [11]. The gestational decline of maternal adiponectin concentration is believed to result from inhibition of the *ADIPOQ* gene transcriptional activity [29], an effect which is even more prominent in GDM pregnancy.

Regulation of ADIPOQ Transcription

Two different mRNA products of the gene have been described, one with three and one with four exons (Ensembl: ENST00000320741 and ENST00000444204), the latter possessing an extra non-coding exon located between the first two of the former. In both cases, adiponectin is coded for by the last two exons so the protein products do not differ in their amino acid sequence. Since nothing is known about the role of the different transcripts and for the sake of convenience (considering the published information regarding the regulation of the gene) the three exon variant will be taken for reference in this chapter.

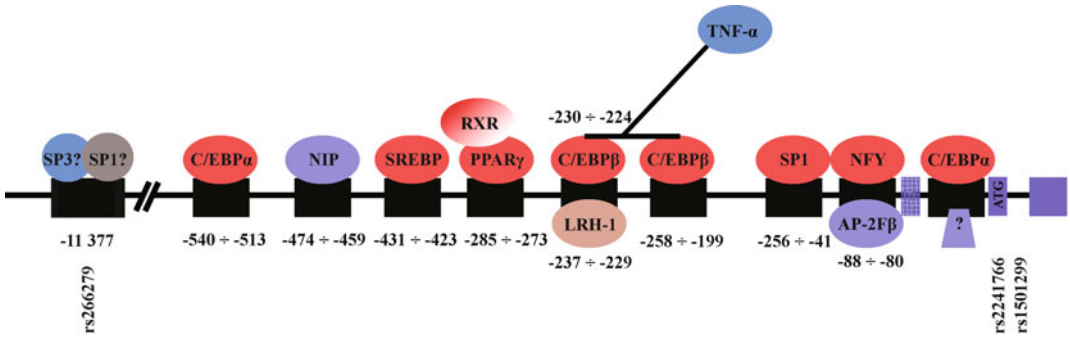


Fig. 11.3 Summary diagram (not to scale) of the most important regulatory elements responsible for the basal transcription and the cell specificity of the *ADIPOQ* expression. *Blue squares* to the *right* designate the three exons (the first, which is noncoding is checkered, the second contains the ATG). *Black squares* are used to show the relative localization of the *cis* regulatory elements. Their precise position, with the exception of those in the intron sequences, are shown with digits. *Red ellipses* distinguish the activating *trans*-factors, while the repressors are shown with *blue–gray*. The *beige* color of LRH-1 and the *gradient red* of RXR demonstrate their lack of independent function and the fact that they act as co-activators for PPARα. The relative location of the three single nucleotide elements subject of the genetic association study carried out by our team are shown at the *bottom* [44]. The *left-most circles* in *blue* and *gray* show putative transcription factors hypothesized to recognize and bind the sequence surrounding rs266729. Question marks are used for *trans*-factors which have not been identified or are just suspected to participate in the regulation of *ADIPOQ* expression

During the last decade, we have gathered a lot of data regarding the mechanisms governing adiponectin's expression. A number of *cis*-elements, *trans*-factors, and modifiers involved in human *ADIPOQ* regulation have been identified. A summary diagram of the most essential regulatory regions in the human adiponectin promoter is shown in Fig. 11.3.

In vitro analyses carried out by Kita and co-authors demonstrate that the sequence between −676 and +41 is sufficient for ensuring a basal expression of the adiponectin gene [30]. This region was found to contain recognition sites for sterol regulatory element binding proteins (SREBP) between −431 and −423, and CCAAT/enhancer binding protein β (C/EBPβ) between −230 and −224. SREBPs are transcription activators involved in adipose tissue differentiation and lipid homeostasis. C/EBPβ is another transcription factor with key role for adipose tissue proliferation and differentiation. Its binding to a putative proximal sequences in the *ADIPOQ* gene located between −258 and −199 seems to be important for mediation of the TNF-α repression [30]. Another CCAAT element, one targeted by C/EBPα, has been identified in a distal enhancer-response element located between −540 and −513 bp [31].

Prompted by the activating effect of thiazolidinediones, agonists of peroxisome proliferator-activated receptor-gamma (PPARγ), on adiponectin expression in animal model, Iwaki and co-authors discovered the existence of PPARγ responsive element (PPRE) in human adiponectin promoter [32]. PPRE is located in position −285 to −273 and is recognized by PPARγ in cooperation with the retinoid X receptor (RXR). PPARγ is a nuclear receptor which is induced by peroxisome proliferators and consequently binds regulatory elements in DNA, thus modulating the transcription of its target genes. Amongst its activators are the free fatty acids, while its effectors include the acyl-CoA oxidase gene. This allows PPARγ to influence the lipid metabolism, making it a key regulator of adipocyte differentiation and glucose homeostasis.

Iwaki et al. discovered an additional *ADIPOQ* regulatory element targeted by another nuclear receptor, namely the liver receptor homolog-1 (LRH-1). Its binding sequence is located in a 3′ direction from PPRE, at position −237 to −229. In vitro studies showed that, while binding of LRH-1 alone has no direct effect on adiponectin expression; it augments the activation triggered by PPARγ/RXR [32].

The overlap between the C/EBPβ and LRH-1 binding sites identified by Kita and Iwaki, respectively, may be explained by putative interaction between the two factors which would allow the adipocytes to respond differently to various metabolic situations by altering the expression of *ADIPOQ*. LRH-1 has been found to inhibit C/EBPβ-mediated transcriptional activation by reducing its binding to elements in the promoters of genes involved in hepatic acute phase response [33]. A positive interaction between the two transcription factors has also been described in the case of LRH-1's own gene [34].

Another activator of *ADIPOQ* expression is SP1 which binds an element located between −256 and −41 bp 5′ of the transcription start site [35]. The SP1—DNA interaction is attenuated by TNF-α which is yet another explanation of the inhibitory effect of the latter on adiponectin expression.

Other transcription factors which may contribute to the proper cell-specific expression and metabolic signal responsiveness of the adiponectin gene are NF-Y and AP-2β [36, 37]. It has been proposed that both factors are competing for the same enhancer elements located between 88 and 80 bp before the transcription start site, in close proximity to a C/EBPβ site, with AP-2β exerting negative and NF-Y positive effect on the transcription. The inhibitory effect of AP-2β on *ADIPOQ* has been confirmed in expression studies [38].

The repressive effect of insulin on adiponectin expression appears to be mediated by a NIP element located between 474 and 459 bp 5′ from the transcription initiation site [39].

Elements with strong influence on the expression and cell specificity of the *ADIPOQ* gene are also found in intron 1 [40]. Several CCAAT elements targeted by C/EBPα were identified in the region +1346 ÷ +10,322 and appear to be essential for the basal transcription of the gene. The same study also found a repressor element located between +3175 and +5993.

The adiponectin promoter is also subjected to epigenetic regulation [19, 41]. Differences in methylation frequencies have been observed for multiple sites within the adiponectin promoter in overweight, obese and morbidly obese children as well as pregnant women with or without glucose intolerance.

Despite the accumulation of substantial knowledge about the general mechanisms for *ADIPOQ* activation and suppression in man, the fine tuning of its transcription under normal physiological changes such as pregnancy or its dysregulation in case of pathology is still not well understood.

Genetic Associations Linking ADIPOQ Regulation and GDM Risk

In 2008–2012, our team carried out a large-scale study involving more than 200 pregnant women with the goal to evaluate the applicability of a number of immunological, biochemical, and genetic markers for the identification of women at risk for gestational diabetes, early diagnosis of the condition and consequently, better prevention of the associated complications. The women were referred to our clinic because of their increased risk for GDM judging by family history of diabetes, obesity before conception, history of reproductive failure, GDM in previous pregnancy followed by normoglycemia after delivery, polycystic ovarian syndrome (PCOS), delivery of fetus with weight >4000 g, ultrasound parameters for macrosomia, multiparity, and/or maternal age >30 years.

The participants were initially tested for glucose intolerance in gestational week 24–28 using the standardized protocols approved by the International Association of Diabetes Pregnancy Study Group (IADPSG) in order to determine their GDM status. They were later subjected to a panel of immunological and biochemical tests, followed by genotyping for single nucleotide polymorphisms in genes known or suspected to influence the individual's risk for this condition such as those for insulin (*INS*), insulin receptor substrate 1 (*IRS1*), glucokinase, glucokinase regulatory protein (*GCKR*), PPAR γ, mannose binding lectin 2 as well as adiponectin and leptin to name but a few.

Among the most important biochemical findings were the consistent differences in adiponectin and leptin levels between GDM women and controls both during pregnancy and postpartum [27]. Significant differences between the two groups were also observed in respect to apelin concentrations but not resistin or visfatin.

The genetic studies confirmed some previously known relationships, like the association of the rs780094 variant in *GCKR* with immunoreactive insulin levels ($p = 0.00777$; number of subjects n = 242) and HOMA index ($p = 0.00629$; n = 242). At the same time, a number of new relationships became apparent, such as the association of an *INS* variant, rs689, which is in linkage disequilibrium with a functional promoter microsatelite known to affect *INS* expression and the serum levels of leptin ($p = 0.00577$; n = 153). The later finding probably reflects the regulatory effects of insulin on leptin promoter [42, 43]. Another interesting novel observation was the association of the rs1800450 variant in MBL2 with blood glucose levels ($p = 0.00697$; n = 242).

Of particular relevance to the topic of this chapter is the observation that a variant affecting known regulatory region in the *AIPOQ* promoter, namely rs266729, is associated with GDM—a finding that links the rise of glucose intolerance in pregnancy with dysregulation of the adiponectin gene [44]. Our interest in studying the contribution of adiponectin gene variants to the individual's risk for gestational diabetes was triggered by the mounting evidence for the essential role of this adipokine in the etiology of this condition. We chose to evaluate three single nucleotide variants which have been shown previously to be associated with metabolic syndrome, obesity, diabetes type 2 or GDM, namely rs266729 (−11377 C > G) located in the promoter region; rs2241766 in exon 2 (+45 T > G; Gly15Gly) and rs1501299 in intron 2 (+276G > T). Their minor allele and genotype frequencies were determined by routine genotyping methods in three groups of women—pregnant normoglycemic (n = 130 individuals), pregnant with GDM (n = 130) and population controls (GDM status not known, n = 134).

Association with gestational diabetes mellitus was found using case/control and alternate/full model association testing for the promoter variant only (see Table 11.2). Statistically, significant differences in the frequency of the minor allele (G) were observed when comparing the GDM group with the combined control group ($p = 0.0037$), the pregnant control group ($p = 0.0274$), and the population control group ($p = 0.0035$). The odds ratio values calculated for each comparison show

Table 11.2 Genotypic analysis for rs266729

Test	MAF/GR affected	MAF/GR unaffected	MAF/GR affected	MAF/GR unaffected	MAF/GR affected	MAF/GR unaffected
	GDM versus combined controls		GDM versus pregnant controls		GDM versus population controls	
Association (G vs. C)	0.215	0.315	0.215	0.3	0.215	0.329
p (corr. p) OR	**0.0037 (0.011) OR: 0.598**		**0.0274**(0.0821) **OR: 0.641**		**0.0035 (0.0106) OR: 0.559**	
Genotypic (2) GG versus GC versus CC	6/44/80	30/103/126	6/44/80	14/50/66	6/44/80	16/53/60
p (corr. p)	**0.0178**		0.0852		**0.0163**	
Dominant (1) GG + GC versus CC	50/80	133/126	50/80	64/66	50/80	69/60
p (corr. p)	**0.0163**		0.0802		**0.0153**	
Recessive (1) GG versus GC + CC	6/124	30/229	6/124	14/116	6/124	16/113
p (corr. p)	**0.0253**		0.0626		**0.0246**	

Comparison between GDM patient and combined, pregnant or population controls, respectively, is shown. The following abbreviations were used: *GDM* individuals with gestational diabetes; *MAF* minor allele frequency; *GR* respective genotype ratios (GG vs. GC vs. CC); *p* nominal p-value; corr. *p* p-value after Bonferroni single step adjusted value; *OR* odds ratio, shown where applicable. The respective degree of freedom for the genotypic, dominant and recessive tests are shown in brackets in each test's cell

that the G allele confers certain degree of protection (OR = 0.598 for GDM vs. combined controls; OR = 0.641 for GDM vs. Pregnant Controls and OR = 0.559 for GDM vs. Population Controls). The association remained significant after Bonferroni multiple test adjustment for GDM versus Combined Control group ($p = 0.011$) and GDM versus Population Control group ($p = 0.0106$).

The association testing used for comparing genotype frequencies under the genotypic, dominant, or recessive model also showed significant differences for GDM women vs Combined Control group and Population Controls for all models with p-values lower than 0.05 observed for all association models—genotypic (GG vs. GC vs. CC), dominant (GG plus GC vs. CC), and recessive (GG vs. GC plus CC).

The genotype data for all three adiponectin polymorphisms allowed us also to carry out haplotype association testing. One particular combination, GTG, formed by the minor allele of the promoter variant, rs266729, and the major alleles of the two intragenic variants, rs2241766 and rs1501299 was found to be statistically less frequent among GDM women in comparison to the Combined Control Group ($p = 0.004$), Population Controls ($p = 0.006$) and Pregnant Controls ($p = 0.022$, respectively) (Table 11.3).

Putative Role of ADIPOQ Dysregulation During Pregnancy

When attempting to understand the biological meaning of the association between rs266729 and GDM observed in our study, we need to make an overview of the available information regarding that particular sequence of the *ADIPOQ* promoter. This genetic variant, undoubtedly because of its location upstream of the transcription initiation site, has been in the focus of interest in a large number of association studies. Unfortunately, the results published by the different groups are somewhat conflicting. For example, some studies find that the minor G allele is associated with decreased adiponectin levels, higher fasting glucose, insulin resistance, obesity, type 2 diabetes, diabetic nephropathy, and metabolic syndrome in both Caucasian and Asian populations [45–47], while others observe an association of the C/C genotype or the C allele with type 2 diabetes, lower insulin sensitivity, morbid obesity, gestational diabetes, and increased fasting glucose levels in type 2 diabetes in the same ethnic groups [48, 49]. Third group of studies report still no association between rs266729 and insulin resistance, adiponectin levels, or gestational diabetes [50–53].

Table 11.3 Haplotype frequencies for the three adiponectin SNPs in the orderrs266729, rs2241766 and rs1501299

Haplotype	Haplotype frequency in			
	GDM	Combined controls	Pregnant controls	Population controls
GTT	0.02	0.02	0.02	0.03
p-value		0.451	0.677	0.327
CTT	0.34	0.26	0.26	0.27
p-value		**0.035**	0.066	0.074
GGG	0.02	0.02	0.01	0.02
p-value		0.828	0.715	0.924
CGG	0.11	0.09	0.09	0.09
p-value		0.286	0.308	0.447
GTG	0.18	0.27	0.27	0.28
p-value		**0.004**	**0.022**	**0.006**
CTG	0.33	0.33	0.35	0.31
		0.944	0.699	0.599

GDM designates individuals with gestational diabetes

It has been found that the rs266729 promoter variant affects the expression of *ADIPOQ* which led to the suggestion that the nucleotide substitution alters a SP1 transcription factor binding site [47]. While the transcription factor recognizing the sequence around position −11,377 has not been identified yet, electro mobility shift assays have proven that the introduction of the minor G allele affects the binding of adipocyte nuclear extract proteins to that nucleotide stretch [46, 48].

Regulation of eukaryote gene expression is a complex process requiring the collaboration of tissue-specific and general transcription factors, histone modifiers, and various common and gene-specific DNA elements. SP1, which has been proposed to bind the sequence where rs266729 is located, is ubiquitous transcription factor, characterized with cell and tissue-specific variability of its expression levels. While generally believed to activate transcription, it can also act as gene repressor depending on its partners. In addition, SP1 is known to share binding sites with other transcription factors, which may compete with it and modify its effect on the target genes. Such interchange has been described for a number of genes and the adiponectin promoter in particular where SP1 activates transcription and SP3 suppresses it [35].

As discussed before, gestation is associated with changes in the activity of *ADIPOQ* in response to the needs of the fetus. This decrease of expression most likely follows altered activity and/or binding of certain regulatory factors. Based on the results from our study in GDM and normoglycemic pregnant women, we propose that the sequence containing the rs266729 polymorphism may play different role in pregnant and nonpregnant women. We hypothesize that the G allele, found by many to decrease the expression of *ADIPOQ* in both males and nonpregnant females, may render the promoter less responsive to the inhibition normally associated with gestation (for example, by hindering SP3-mediated suppression). This effect could be strengthened by the combined inheritance of the rs266729 variant and the major alleles of the other two single nucleotide polymorphisms rs2241766 and rs1501299, found to be associated with increased levels of adiponectin and greater insulin sensitivity [54]. The association of the GTG haplotype with GDM observed in our study is one indication for such interaction. Such protective effect of the minor G allele of rs266729 in pregnancy may explain the relatively high frequency of this genetic variant in the general population despite its association with increased risk for metabolic syndrome and type 2 diabetes.

Recommendations and Guidelines

The key to successful treatment of GDM and prevention of its complications is our ability to accurately identify pregnant women predisposed to developing this condition. At present, leading healthcare institutions base their risk assessment on baseline maternal characteristics, such as BMI, family or personal history, ethnicity, etc. which is both limited and not sufficiently accurate approach [55, 56]. Fasting plasma glucose, response to glucose challenge, fructosamine, or $HbA_{1c,}$ are deemed unsuitable as stratifying markers and their use is not recommended. The identification of first trimester biomarker(s) with high sensitivity and sufficient specificity will allow targeted care for the at-risk women and early intervention for tackling insulin resistance and avoiding complications [28]. Best suited for this role would be molecules which are directly involved in the pathogenesis of GDM, because changes in their expression would be a direct indicator for the presence of pathological processes. Such markers would be ideal as early warning signs especially if they are readily detectable with noninvasive methods. Adiponectin appears to meet these requirements. What is more, its predicative value has already been evaluated and proven [28]. Large prospective studies for confirmation of the preliminary research data have been called for and are expected to provide the grounds for specific guidelines for GDM risk assessment based on the adiponectin levels. It is recommended that the medical establishments, particularly the clinics involved in maternal and fetal health care with their expertise and position, should undertake these investigations. The successful completion of the

studies would require efforts for identifying the most appropriate technique, optimizing the methodology and recruiting sufficiently large sample groups. Given the significant interethnic variability in plasma adiponectin levels, the involvement of pregnant women with different origin is recommended for determining cutoff values that will allow accurate distinction between normal and GDM pregnancies in different populations [15]. Such prospective study, albeit on a small scale, was carried out in the Clinical Center of Endocrinology, USBALE "Acad. Iv. Pentchev," Medical University of Sofia, and allowed us to determine reference values which may be used for initial testing of risk stratification protocol [27].

Conclusions

In this chapter, we presented the results from a large-scale association study of gestational diabetic mellitus involving almost 400 women and carried out by our group [44]. Reviewing the data in the context of the current scientific knowledge for adiponectin and its biological role for maintaining the energy homeostasis in the organism allowed us to form a hypothesis linking dysregulation of its expression with gestational diabetes mellitus. Proving this theory would require additional in vitro and in vivo functional studies using appropriate model systems. These investigations would need to (1) identify the transcription factor(s) binding to the sequence affected by rs266729, (2) determine whether there is indeed change in its (their) binding affinity to that regulatory sequence during pregnancy, (3) check if this binding is affected by the presence of the alternative allele, (4) determine whether there are other transcription factors with modifying effect recognizing the same sequence and competing with it during pregnancy or under other physiological conditions associated with metabolic changes, and (5) establish how are these "additional" *trans* acting proteins affected by the single nucleotide polymorphism in position −11,377.

As years of research have clearly demonstrated, GDM results from complex interactions between environmental and genetic factors. The effects of the three *ADIPOQ* variants we focused on in our study probably contribute little to the individual's risk for GDM. They may, however, have an additive effect together with other common polymorphisms in genes with important role for the carbohydrate and lipid metabolism. Large-scale genetic epidemiology studies would need to be conducted in order to understand better the interaction of polymorphisms and variants in other genes known to contribute to the GDM pathology as well as environmental effects like diet, weight gain, and physical activity.

Acknowledgements The authors' work presented here has been funded under grants: DO 02/7 2008 National science fund, Ministry of Education and Science, Entitled: "Contemporary approach for diagnostics, frequency assessment and genotype-phenotype correlations in patients with gestational diabetes mellitus in Bulgarian population"; 11 D/2010 Medical University Sofia, Entitled: "Adipocytokines in normal and complicated with gestational diabetes pregnancy"; DUNK01-2/2009, National science fund, Ministry of Education and Science, Entitled: "National University Research Complex for Biomedical and Translational Research".

References

1. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J clin Endocrinol Metab. 2007;92(3):1023–33.
2. Miehle K, Stepan H, Fasshauer M. Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia. Clin Endocrinol. 2012;76(1):2–11.
3. Abell SK, De Courten B, Boyle JA, Teede HJ. Inflammatory and other biomarkers: role in pathophysiology and prediction of gestational diabetes mellitus. Int J Mol Sci. 2015;16(6):13442–73.

4. Bao W, Baecker A, Song Y, Kiely M, Liu S, Zhang C. Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: a systematic review. Metab Clin Exp. 2015;64(6): 756–64.
5. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7(8):941–6.
6. Bailey CJ, Tahrani AA, Barnett AH. Future glucose-lowering drugs for type 2 diabetes. Lancet Diab Endocrinol. 2016.
7. Liu M, Zhou L, Xu A, et al. A disulfide-bond A oxidoreductase-like protein (DsbA-L) regulates adiponectin multimerization. Proc Natl Acad Sci USA. 2008;105(47):18302–7.
8. Pajvani UB, Hawkins M, Combs TP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem. 2004;279(13):12152–62.
9. Waki H, Yamauchi T, Kamon J, et al. Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. J Biol Chem. 2003;278(41):40352–63.
10. Bobbert P, Antoniak S, Schultheiss HP, Rauch U. Globular adiponectin but not full-length adiponectin induces increased procoagulability in human endothelial cells. J Mol Cell Cardiol. 2008;44(2):388–94.
11. Aye IL, Powell TL, Jansson T. Review: Adiponectin–the missing link between maternal adiposity, placental transport and fetal growth? Placenta. 2013;34(Suppl):S40–5.
12. Tanabe H, Fujii Y, Okada-Iwabu M, et al. Crystal structures of the human adiponectin receptors. Nature. 2015; 520(7547):312–6.
13. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003;423(6941):762–9.
14. Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. J Mol Cell Biol. 2016.
15. Chen X, Scholl TO. Ethnic differences in maternal adipokines during normal pregnancy. Int J Environ Res Public Health. 2015;13(1).
16. Chan TF, Yuan SS, Chen HS, et al. Correlations between umbilical and maternal serum adiponectin levels and neonatal birthweights. Acta Obstet Gynecol Scand. 2004;83(2):165–9.
17. Kajantie E, Hytinantti T, Hovi P, Andersson S. Cord plasma adiponectin: a 20-fold rise between 24 weeks gestation and term. J Clin Endocrinol Metab. 2004;89(8):4031–6.
18. Chen J, Tan B, Karteris E, et al. Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. Diabetologia. 2006;49(6):1292–302.
19. Bouchard L, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration. Diabetes. 2012;61(5):1272–80.
20. Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression. Am J Physiol Endocrinol Metab. 2006;290(2):E326–33.
21. Lappas M, Yee K, Permezel M, Rice GE. Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies. J Endocrinol. 2005;186(3):457–65.
22. Aye IL, Gao X, Weintraub ST, Jansson T, Powell TL. Adiponectin inhibits insulin function in primary trophoblasts by PPARalpha-mediated ceramide synthesis. Mol Endocrinol. 2014;28(4):512–24.
23. Jones HN, Jansson T, Powell TL. Full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino Acid transport in human primary trophoblast cells. Diabetes. 2010;59(5):1161–70.
24. Rosario FJ, Schumacher MA, Jiang J, Kanai Y, Powell TL, Jansson T. Chronic maternal infusion of full-length adiponectin in pregnant mice down-regulates placental amino acid transporter activity and expression and decreases fetal growth. J Physiol. 2012;590(6):1495–509.
25. Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ, Zinman B. Low adiponectin concentration during pregnancy predicts postpartum insulin resistance, beta cell dysfunction and fasting glycaemia. Diabetologia. 2010;53(2):268–76.
26. Williams MA, Qiu C, Muy-Rivera M, Vadachkoria S, Song T, Luthy DA. Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. J Clin Endocrinol Metab. 2004;89(5): 2306–11.
27. Boyadzhieva M, Atanasova I, Zacharieva S, Kedikova S. Adipocytokines during pregnancy and postpartum in women with gestational diabetes and healthy controls. J Endocrinol Invest. 2013;36(11):944–9.
28. Iliodromiti S, Sassarini J, Kelsey TW, Lindsay RS, Sattar N, Nelson SM. Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis. Diabetologia. 2016;59(4):692–9.
29. Catalano PM, Hoegh M, Minium J, et al. Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. Diabetologia. 2006;49(7):1677–85.
30. Kita A, Yamasaki H, Kuwahara H, et al. Identification of the promoter region required for human adiponectin gene transcription: Association with CCAAT/enhancer binding protein-beta and tumor necrosis factor-alpha. Biochem Biophys Res Commun. 2005;331(2):484–90.

31. Segawa K, Matsuda M, Fukuhara A, et al. Identification of a novel distal enhancer in human adiponectin gene. J Endocrinol. 2009;200(1):107–16.
32. Iwaki M, Matsuda M, Maeda N, et al. Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. Diabetes. 2003;52(7):1655–63.
33. Venteclef N, Smith JC, Goodwin B, Delerive P. Liver receptor homolog 1 is a negative regulator of the hepatic acute-phase response. Mol Cell Biol. 2006;26(18):6799–807.
34. Hadizadeh S, King DN, Shah S, Sewer MB. Sphingosine-1-phosphate regulates the expression of the liver receptor homologue-1. Mol Cell Endocrinol. 2008;283(1–2):104–13.
35. Barth N, Langmann T, Scholmerich J, Schmitz G, Schaffler A. Identification of regulatory elements in the human adipose most abundant gene transcript-1 (apM-1) promoter: role of SP1/SP3 and TNF-alpha as regulatory pathways. Diabetologia. 2002;45(10):1425–33.
36. Ikeda K, Maegawa H, Ugi S, et al. Transcription factor activating enhancer-binding protein-2beta. A negative regulator of adiponectin gene expression. J Biol Chem. 2006;281(42):31245–53.
37. Park SK, Oh SY, Lee MY, Yoon S, Kim KS, Kim JW. CCAAT/enhancer binding protein and nuclear factor-Y regulate adiponectin gene expression in adipose tissue. Diabetes. 2004;53(11):2757–66.
38. Meng X, Kondo M, Morino K, et al. Transcription factor AP-2beta: a negative regulator of IRS-1 gene expression. Biochem Biophys Res Commun. 2010;392(4):526–32.
39. Sun X, He J, Mao C, et al. Negative regulation of adiponectin receptor 1 promoter by insulin via a repressive nuclear inhibitory protein element. FEBS Lett. 2008;582(23–24):3401–7.
40. Qiao L, Maclean PS, Schaack J, et al. C/EBPalpha regulates human adiponectin gene transcription through an intronic enhancer. Diabetes. 2005;54(6):1744–54.
41. Garcia-Cardona MC, Huang F, Garcia-Vivas JM, et al. DNA methylation of leptin and adiponectin promoters in children is reduced by the combined presence of obesity and insulin resistance. Int J Obes. 2014;38(11):1457–65.
42. Maymo JL, Perez Perez A, Gambino Y, Calvo JC, Sanchez-Margalet V, Varone CL. Review: leptin gene expression in the placenta–regulation of a key hormone in trophoblast proliferation and survival. Placenta. 2011;32 Suppl 2:S146–53.
43. Wang FN, Ma CG, Zhang YL, et al. Identification of glucose-responsive and insulin-responsive elements in promoter of mouse ob gene. Sheng wu hua xue yu sheng wu wu li xue bao Acta biochimica et biophysica Sinica. 2000;32(5):541–4.
44. Beltcheva O, Boyadzhieva M, Angelova O, Mitev V, Kaneva R, Atanasova I. The rs266729 single-nucleotide polymorphism in the adiponectin gene shows association with gestational diabetes. Arch Gynecol Obstet. 2014;289(4):743–8.
45. Buzzetti R, Petrone A, Zavarella S, et al. The glucose clamp reveals an association between adiponectin gene polymorphisms and insulin sensitivity in obese subjects. Int J Obes. 2007;31(3):424–8.
46. Laumen H, Saningong AD, Heid IM, et al. Functional characterization of promoter variants of the adiponectin gene complemented by epidemiological data. Diabetes. 2009;58(4):984–91.
47. Zhang D, Ma J, Brismar K, Efendic S, Gu HF. A single nucleotide polymorphism alters the sequence of SP1 binding site in the adiponectin promoter region and is associated with diabetic nephropathy among type 1 diabetic patients in the genetics of kidneys in diabetes study. J Diab Complications. 2009;23(4):265–72.
48. Bouatia-Naji N, Meyre D, Lobbens S, et al. ACDC/adiponectin polymorphisms are associated with severe childhood and adult obesity. Diabetes. 2006;55(2):545–50.
49. Populaire C, Mori Y, Dina C, et al. Does the -11377 promoter variant of APM1 gene contribute to the genetic risk for Type 2 diabetes mellitus in Japanese families? Diabetologia. 2003;46(3):443–5.
50. Chiodini BD, Specchia C, Gori F, et al. Adiponectin gene polymorphisms and their effect on the risk of myocardial infarction and type 2 diabetes: an association study in an Italian population. Ther Adv Cardiovasc Dis. 2010;4 (4):223–30.
51. Chung HK, Chae JS, Hyun YJ, et al. Influence of adiponectin gene polymorphisms on adiponectin level and insulin resistance index in response to dietary intervention in overweight-obese patients with impaired fasting glucose or newly diagnosed type 2 diabetes. Diab Care. 2009;32(4):552–8.
52. Gueuvoghlanian-Silva BY, Torloni MR, Mattar R, et al. Profile of inflammatory mediators in gestational diabetes mellitus: phenotype and genotype. Am J Reprod Immunol. 2012;67(3):241–50.
53. Wang Y, Zhang D, Liu Y, et al. Association study of the single nucleotide polymorphisms in adiponectin-associated genes with type 2 diabetes in Han Chinese. J Genet Genomics = Yi chuan xue bao. 2009;36(7):417–23.
54. Enns JE, Taylor CG, Zahradka P. Variations in adipokine genes AdipoQ, Lep, and LepR are associated with risk for obesity-related metabolic disease: the modulatory role of gene-nutrient interactions. J Obes. 2011;2011:168659.
55. Fasshauer M, Bluher M, Stumvoll M. Adipokines in gestational diabetes. Lancet Diab Endocrinol. 2014;2(6):488–99.
56. Excellence NIfHaC. Diabetes in pregnancy: management from preconception to the postnatal period (London N, editor). NICE guideline; 2015.

Chapter 12
The Retinol Binding Protein-4 (RBP4) Gene and Gestational Diabetes

Renata Saucedo, Jorge Valencia, Lourdes Basurto, Marcelino Hernandez, Edgardo Puello, Arturo Zarate, Patricia Mendoza and Patricia Ostrosky

Key Points

- Previous studies have reported that single nucleotide polymorphisms (SNPs) of retinol binding protein 4 (RBP4) could increase diabetes susceptibility, and decrease insulin secretion and insulin sensitivity.
- RBP4 is thought to affect insulin sensitivity by down-regulating the activities of phosphoinositol-3-kinase and the phosphorylation of insulin in muscles.
- RBP4 can stimulate hepatic gluconeogenesis through stimulation of phosphoenolpyruvate carboxykinase.
- Several genetic variants that affect RBP4 expression levels have been investigated in gestational diabetes mellitus (GDM); however, the reported findings are inconsistent.
- The mechanisms by which noncoding RBP4 variants could decrease insulin secretion are unclear.

R. Saucedo (✉) · J. Valencia · L. Basurto · M. Hernandez · A. Zarate
Endocrine Research Unit, National Medical Center, Mexican Social Security Institute, Cuauhtemoc 330, Mexico City, Mexico
e-mail: sgrenata@yahoo.com

J. Valencia
e-mail: j.valencia.o@hotmail.com

L. Basurto
e-mail: lbasurtoa@yahoo.com

M. Hernandez
e-mail: mhernandezvalencia@prodigy.net.mx

A. Zarate
e-mail: zaratre@att.net.mx

E. Puello
Hospital of Gynecology and Obstetrics, Medical Center La Raza, Mexican Social Security Institute, Calzada Vallejo s/n, Mexico City, Mexico
e-mail: edgardo.puello@imss.gob.mx

P. Mendoza
Laboratory of Molecular Biology and Pharmacogenomics, Juarez Autonomous University of Tabasco, Km 1 Carretera Cunduacan-Jalpa de Mendez, A. P. 24, Cunduacan, Tabasco, Mexico
e-mail: patricia.mendoza@ujat.mx

P. Ostrosky
Department of Genomic Medicine and Environmental Toxicology, Instituto de Investigaciones Biomedicas, Autonomous National University of Mexico, Av Universidad 3000, Mexico City, Mexico
e-mail: ostrosky@servidor.unam.mx

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_12

- The sample size of the studies has been relatively small and the significance of the associations has been relatively modest.
- The possibility cannot be excluded that the effect of the SNP′s could be due to a nearby gene in linkage disequilibrium with RBP4.

Keywords Retinol binding protein 4 · Single nucleotide polymorphisms · Gestational diabetes mellitus · Vitamin A · Retinol · Type 2 diabetes

Abbreviations

GDM	Gestational diabetes mellitus
GLUT4	Glucose transporter 4
GPR120	G protein-coupled receptor 120
HDL	High-density lipoprotein
PDE6C	Phosphodiesterase 6C, cGMP-specific, cone, alpha prime
PEPCK	Phosphoenolpyruvate carboxykinase
RBP4	Retinol binding protein 4
SNPs	Single nucleotide polymorphisms
TTR	Transthyretin
T2D	Type 2 diabetes

Introduction

Control of blood glucose levels depends on the efficient action of insulin. Liver, skeletal muscle and adipose tissue are the major targets for the metabolic actions of insulin. Insulin regulates glucose homeostasis by reducing hepatic glucose output and by increasing the rate of glucose uptake by skeletal muscle and adipose tissue.

Insulin resistance is a failure of target organs to respond normally to the action of insulin. Insulin resistance causes incomplete suppression of hepatic glucose output and impaired insulin-mediated glucose uptake in the periphery, leading to increased insulin requirements. When increased insulin requirements are not matched by increased insulin levels, hyperglycemia develops. An impaired insulin action predisposes individuals to type 2 diabetes (T2D) and it is also a major risk factor for cardiovascular disease.

Obesity is a major cause of insulin resistance; however, its exact mechanism is still a subject of ongoing research. In addition, being an energy depot, adipose tissue is an active endocrine organ that secretes a variety of proteins, known as “adipokines”. Adipokines affect distant tissues and play key roles in essential physiological functions such as regulation of appetite, body weight and energy expenditure. Some of these adipokines have been implicated in the development of insulin resistance. They may act locally or distally to alter insulin sensitivity in insulin-targeted organs such as muscle and liver, or may act through neuroendocrine, autonomic, or immune pathways. Such adipokines include tumor necrosis factor, interleukin 6, plasminogen activator inhibitor-1, resistin, leptin, adiponectin and, as recently reported, retinol binding protein 4 (RBP4), the specific carrier for retinol in the blood.

Vitamin A

Vitamin A is a fat-soluble vitamin that is essential for humans and other vertebrates. Vitamin A comprises a family of molecules containing a 20 carbon structure with a methyl-substituted cyclohexenyl ring (beta-ionone ring) and a tetraene side chain with a hydroxyl group (retinol), aldehyde group (retinal), carboxylic acid group (retinoic acid), or ester group (retinyl ester) at carbon-15. The term vitamin A includes provitamin A carotenoids that are dietary precursors of retinol [1].

There are a number of sources of dietary vitamin A. Preformed vitamin A is abundant in some animal-derived foods, whereas provitamin A carotenoids are abundant in darkly colored fruits and vegetables, as well as oily fruits and red palm oil [2]. Vitamin A is obtained as retinol esters and goes along the chylomicrons to the liver [3]. Part of the retinol esters are readily hydrolyzed to retinol, which binds to RBP4 [4].

Vitamin A is important for normal vision, gene expression, reproduction, embryonic development, growth, and immune function (Fig. 12.1) [5]. The most specific clinical effect of inadequate vitamin A intake is xerophthalmia. Vitamin A deficiency has been associated with a reduction in lymphocyte numbers, natural killer cells, and antigen-specific immunoglobulin responses [6].

Vitamin A deficiency is an endemic nutrition problem throughout much of the developing world, especially affecting the health and survival of infants, young children, and pregnant and lactating women. According to the World Health Organization, globally, 15.3% (7.4–23.2) of pregnant women (19.1 million women) have deficient serum retinol concentrations [7]. In our country, according to data of a large nationally representative nutrition survey, vitamin A depletion was detected in 4% of women of reproductive age [8].

Pregnancy is associated with progressive insulin resistance, which begins during mid-pregnancy and progresses throughout the third trimester. Gestational diabetes mellitus (GDM) is described as glucose intolerance of variable intensities that begins or is first diagnosed during pregnancy and usually resolves during the first postpartum weeks [9]. It is generally accepted that women with GDM exhibit eminent insulin resistance and are at high risk for developing T2D after delivery [10].

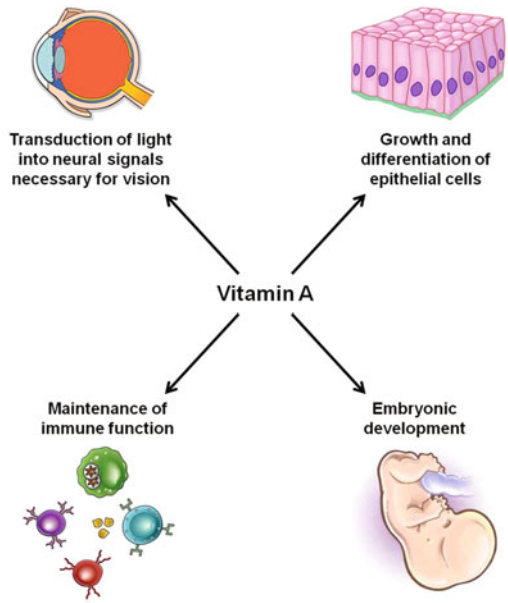


Fig. 12.1 Vitamin A functions. Vitamin A is essential for the maintenance of normal vision, promotes growth of epithelial cells and other cell types in the body, is involved in the embryonic development and contributes to a normal function of the immune system

Literature shows conflicting information on concentrations of retinol in women affected by GDM, since some studies reported reductions, while others did not [11, 12].

Retinol Binding Protein 4 (RBP4)

Action and Clearance

RBP4 is a 21 kDa plasma protein, which belongs to the lipocalin family and is the specific carrier for retinol in the blood. It delivers retinol from the liver stores to the peripheral tissues. The binding of retinol to RBP4 guarantees the homeostatic regulation of plasma retinol levels. RBP4 circulates in serum, forming a 1:1:1 complex with retinol and transthyretin (TTR), a transport protein for thyroxine (Fig. 12.2). The affinity of RBP4-TTR binding is very strong, and there is little or no free RBP4. The binding with TTR increases the molecular weight of RBP4 and thus prevents its glomerular filtration and catabolism in the kidney. After releasing retinol into the target cells, the remaining apo-RBP4 (unbound retinol) is rapidly filtered through the glomeruli and subsequently reabsorbed in the proximal tubular cells via the megalin-cubulin receptor complex and catabolized. Importantly, dysfunctions of both, the liver and kidneys, are known to influence RBP4 homeostasis: chronic kidney diseases and chronic liver diseases interfere with RBP4 metabolism through their action on RBP4 synthesis and catabolism [13].

Synthesis

Hepatocytes are the principal cells producing RBP4 under normal metabolic conditions, and adipose tissue has the second highest expression level of RBP4. However, in the insulin resistant state, adipose tissue has 2.3-fold greater RBP4 mRNA and these levels have been estimated to be equivalent with liver expression [14].

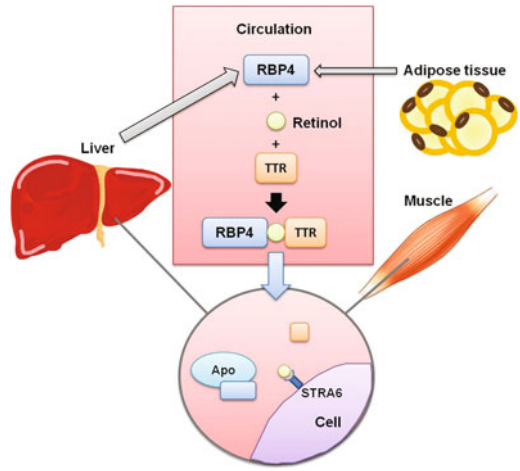


Fig. 12.2 Synthesis and action of retinol binding protein 4 (RBP4). Retinol binding protein 4 (RBP4) is predominantly synthetized in the liver, with a lesser amount derived from adipose tissue. It circulates in serum, forming a 1:1:1 complex with retinol and transthyretin (TTR). RBP4 delivers retinol from the liver stores to the peripheral tissues; RBP4 that is not bound to retinol is called Apo-RBP4. Retinol enters cells mainly through the interaction with its receptor STRA6, which is expressed in muscle and liver

Isoforms

RBP4 has been reported to occur in different isoforms in serum, namely holo-RBP4 (RBP4 bound to retinol) and apo-RBP4, which remains after the release of retinol into the target cell. In addition, there are other RBP4 isoforms resulting from the truncation of RBP4. RBP4-L, which is truncated at one C-terminal leucine molecule (Leu-183), and RBP4-LL, which is truncated at a second leucine molecule (Leu-182 and Leu-183). The relative amounts of apo-RBP4 are increased in rats during acute renal failure and RBP4-L and RBP4-LL have been shown to be increased in hemodialysis patients. It is assumed that renal dysfunction is closely linked to an increased occurrence of apo-RBP4, as well as RBP4-L and RBP4-LL, in serum [15].

Receptor

A cell-surface receptor for RBP4 was first described by a number of groups in the mid-1970s [16]. Most recently, two reports have established STRA6 as a cell-surface receptor for retinol-RBP that removes retinol from RBP and transports it across the plasma membrane, where it can be metabolized. STRA6 is expressed in sites of insulin action like muscle and liver [17].

RBP-4 Acting as a Glucose Sensor

RBP4 was established as an adipokine in the 1990s and a causal role for RBP4 in the pathogenesis of insulin resistance and type 2 diabetes has only recently been suggested [18–20].

Recent studies in mice have revealed that RBP4 would explain much of the adipocyte-muscle connection that links obesity and insulin resistance. Although, RBP4 was thought to function only to deliver retinol to peripheral tissues, microarray studies have found high levels of RBP4 expression in the adipose tissue of insulin-resistant glucose transporter-4 (GLUT4) knockout mice [18]. Stimulation of glucose uptake into muscle cells and adipocytes by insulin depends largely on translocation of GLUT4 from an intracellular compartment to the cell surface. The expression of GLUT4 is reduced in adipocytes, but not in skeletal muscle, of animals and humans with obesity and T2D [21].

Yang et al. studied GLUT4 knockout mice and suggested that adipose tissue serves as a glucose sensor and modulates systemic glucose metabolism through release of a substance in response to decreased intracellular glucose concentrations. Further transgenic mice studies manipulating GLUT4 expression have shown corresponding inverse changes in RBP4 adipose tissue expression and circulating RBP4 levels. Through microarrays studies, these researchers found that expression of the gene encoding RBP4 was increased in adipose tissue of mice with adipocyte-specific reduction of GLUT4. These studies demonstrated a mechanism by which adipocytes can modulate glucose metabolism in muscle (Fig. 12.3). [18].

These authors found that increasing the circulating levels of RBP4 resulted in glucose intolerance and, conversely, deleting the RBP4 gene in mice increased insulin sensitivity. They also showed that circulating RBP4 levels were substantially increased not only in several mouse models of obesity and insulin resistance, but also in humans with these conditions. Moreover, rosiglitazone, an insulin-sensitizing drug, reduced the elevated levels of RBP4 in both adipose tissue and serum of mice and normalized insulin sensitivity. Finally, they showed that treatment of mice with the synthetic retinoid fenretinide, which increases the excretion of RBP4, lowering its levels in the blood, ameliorated insulin resistance caused by high-fat feeding [18].

A potential link between RBP4 and human diabetes was suggested by a study that revealed that RBP4 can foretell early stages in the development of insulin resistance [22]. The new findings offered

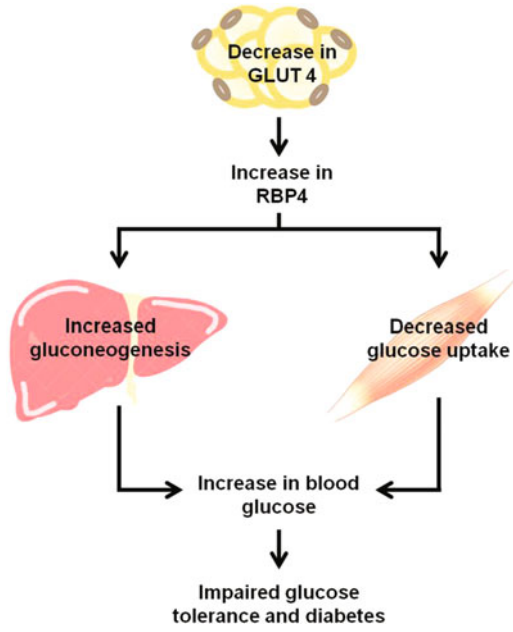


Fig. 12.3 Expression of RBP4 regulates glucose metabolism in liver and skeletal muscle. The decrease in glucose transporter-4 (GLUT4) expression that occurs in adipocytes of animals or humans with obesity and type 2 diabetes is accompanied by increased expression and secretion of RBP4 in adipose tissue. This adipokine upregulates expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) in the liver, interfering with suppression of glucose production, and inhibits insulin signaling in skeletal muscle, inhibiting glucose uptake. The consequent increase in glucose output by the liver and reduction in glucose uptake by muscle result in an increase in blood glucose

a potential new target for the development of anti-diabetic therapies to lower serum RBP4 levels as well as an early means of identifying individuals who were at risk of developing diabetes before the onset of the disease [23].

They first studied individuals with either obesity, impaired glucose tolerance, or with type 2 diabetes, comparing the blood levels of RBP4 in these insulin-resistant subjects with levels found in non-obese healthy subjects. Their results showed that not only were RBP4 levels higher in all cases in which insulin resistance was high, but that elevated serum RBP4 was also closely associated with components of the metabolic syndrome, including increased body mass index, waist-to-hip ratio, serum triglyceride levels, and systolic blood pressure, as well as decreased levels of high-density lipoprotein (HDL). The study was then extended to subjects with normal body weight and normal blood glucose, but with a strong family history of type 2 diabetes. The investigators found elevated RBP4 levels among this group as well [22].

Finally, the authors tested whether exercise could lower RBP4 levels and increase insulin sensitivity. They found that all of the people who improved their insulin sensitivity with exercise also lowered their serum RBP4 levels. Among the one-third of the subjects who did not improve their insulin sensitivity, RBP4 levels did not go down either [22].

Whereas the foregoing account would suggest a major role for RBP4 in diagnosis and treatment of human diabetes, more recent reports have, however, not been so encouraging. Some investigators have found circulating RBP4 levels correlate positively and significantly with insulin resistance [24–27], whereas others have found no relationship between circulating RBP4 and insulin resistance [28–31]. In individuals who are not obese and have no family history of diabetes, or a diagnosis of diabetes, RBP4 is associated with insulin resistance. These results have suggested that in this group of subjects without

strong risk factors for diabetes such as obesity or family history, RBP4 may be used as an index of insulin sensitivity, where currently there are no accurate markers [32].

However in a 3-year longitudinal study in non-diabetic overweight subjects with normal basal fasting glucose and insulin levels, subjects who developed significant insulin resistance showed no change in circulating RBP4 levels [33]. This is evidence that plasma RBP4 is not a good marker of insulin resistance in overweight subjects.

Recently, it has been suggested that the degree of renal impairment is likely to further confound any relationship between circulating RBP4 and insulin resistance [34–36]. Glomerular dysfunction in chronic renal failure can lead to increased circulating RBP4 levels [35, 36] and tubular dysfunction can lead to decreased resorption and elevated RBP4 excretion, thereby compromising serum levels [36]. In a recent study, Raila et al., using matched plasma and urine samples, reported that plasma RBP4 levels in type 2 diabetics were affected by incipient nephropathy [34]. This further tempers consideration of RBP4 as a marker of insulin resistance.

Mechanism of Action

The mechanism by which RBP4 affects insulin action is partially elucidated. In muscle, RBP4 decreases the activity of the phosphoinositol-3 kinase and the phosphorylation of insulin receptor substrate-1, both effects being clear markers of impaired insulin action. Increasing RBP4 does not alter PI-3 kinase activity in liver, yet glucose production in the liver is clearly increased, in concert with increased expression of a key enzyme in the glucose production pathway, phosphoenolpyruvate carboxykinase (PEPCK). However, RBP4 binds to a wide range of retinoids and is likely to transport other lipophilic molecules that may mediate its effect on glucose [18].

Genetics

The RBP4 gene is located on chromosome 10q24, a region where family studies in Mexican Americans and Caucasians have reported linkage to T2D and related clinical characteristics [37, 38]. It is localized between the GPR120 (G protein-coupled receptor 120) and PDE6C (phosphodiesterase 6C, cGMP-specific, cone, alpha prime) genes. RBP4 is composed of six exons; the first four exons are encoded in a CpG island.

Many studies have reported associations between genetic variants at genes encoding adipokines and hyperglycemia, dyslipidemia and obesity. Therefore the RBP4 gene and the correlation between its variants and the risk of type 2 diabetes have been examined.

Munkhtulga et al. screened this gene in a Mongolian population and detected nine single nucleotide polymorphisms (SNPs), all of which were located in the non-coding region. Six of the SNP's were significantly associated with the risk of type 2 diabetes. Furthermore, they found the SNP −803G > A in the promotor region played a functional role by regulating RBP4 gene expression in vitro. The SNP −803G > A, is located at 5 bp downstream of the hepatocyte nuclear factor 1 motif, and could modify gene transcription efficiency by affecting the binding of transcription factors in vitro. The −803A allele induced almost two-fold greater transcriptional activity than the G allele. The genetic risk of diabetes associated with RBP4 was an odds ratio 1.59, 95%CI 1.16–2.23. They provided the first evidence of an association between the RBP4 gene and T2D [39].

Craig et al. examined two populations, Caucasians and African Americans. Although no single SNP was associated with type 2 diabetes, they identified a haplotype comprising 8 common SNPs in Caucasians that was significantly increased in type 2 diabetes relative to controls. They found an

association of individual SNPs with quantitative traits related to glucose homeostasis in nondiabetic subjects, including reduced insulin sensitivity (SNP +390), and reduced insulin secretion (SNP −804, SNP +9476) [40].

Hu C identified ten SNP´s in a Chinese population; however, no individual SNP was significantly associated with type 2 diabetes, although a haplotype CAA formed by +5388 C > T, +8201 T > A and +8204 T > A was more frequent in diabetic patients. Non-coding SNPs in linkage disequilibrium with SNP −803G > A were associated with circulating RBP4 concentrations in both diabetic patients and subjects with normal glucose regulation. They also found that these SNP´s were associated with serum C-peptide concentrations in subjects with normal glucose regulation [41].

Kovacs identified 8 SNPs, and a haplotype of six common SNPs (AGGTGC) was significantly increased in subjects with type 2 diabetes compared with controls. Furthermore, subjects who were carriers of the haplotype had significantly higher mean fasting plasma insulin and 2-h plasma glucose than subjects without the haplotype. Two single SNps (rs10882283 and rs10882273) were also associated with BMI, waist-to-hip ratio, and fasting plasma insulin. In addition, subjects carrying the haplotype had significantly higher mRNA levels in visceral adipose tissue in nondiabetic subjects [42].

van Hoek, in a large prospective population-based study, investigated the effect of the RBP-4 − 803 GA polymorphism on type 2 diabetes risk and provided evidence that homozygosity for the RBP-4 −803A allele is associated with increased risk of T2D [43].

GDM shares several risk factors with T2D and they share similar pathophysiology [10]. Because of these striking parallels, recent work on the etiology of GDM has begun to evaluate the role of common variants in genes predisposing to T2D [44, 45]. Several genetic variants that affect RBP4 expression levels have been investigated in GDM; however, the reported findings are inconsistent [46–48]. In pregnant Chinese women, the variants rs3758539 and rs12265684 were involved in the development of GDM [46]. By contrast, the variant rs3758539 was not found to be associated with GDM in Asian, Pacific Islander women [47] and in Mexican women [48]. Moreover, in a recent meta-analysis, the association between RBP4 rs3758539 polymorphism and GDM was not confirmed [49].

Two other SNPs of RBP4 (rs116736522, and rs34571439) were analyzed in Mexican women by our team. The frequencies of the rare alleles were not significantly different between GDM patients and healthy pregnant women. Also, the SNPs were not associated with lipid profile, and RBP4 levels. However, rs34571431 and rs3758539 showed associations with insulin levels and with insulin resistance in GDM subjects at postpartum [48]. This association is consistent with the results obtained in T2D [39–43].

Our findings revealed that rs34571431 was in linkage disequilibrium with rs3758539. The rs34571431 is located at 5 bp downstream of the hepatocyte nuclear factor 1 motif, and it has been proposed that it could modify gene transcription efficiency by affecting the binding of transcription factors and RBP4 plasma levels. However, we did not find an effect of this polymorphism on serum RBP4 levels [48].

At this time, the mechanism underlying the RBP4 genetic variants and islet B-cell secretion function is unknown. The sample size of the studies has been relatively small and the significance of the associations has been relatively modest. Furthermore the possibility that the effect of the SNP´s could be due to a nearby gene in linkage disequilibrium with RBP4 cannot be excluded.

Recommendations or Guidelines

Vitamin A deficiency is an endemic nutrition problem affecting the health and survival of infants, young children, and pregnant and lactating women. Maternal vitamin A deficiency has been associated with increased low birthweight and infant mortality. It has been suggested that people with lower socioeconomic level have lower accessibility to high quality diets (including foods rich in

vitamin A: eggs, milk, fruits and vegetables), and are at higher risk of being vitamin A deficient. Vitamin A deficiency is of high interest for public nutrition and requires programmatic implementations in order to correct it. Some public health programs have included the administration of oral vitamin A and supplements to people who live in depressed socioeconomic areas; however, the effectiveness of such programs has not been evaluated yet.

On the other hand, extensive research during the past decade according to the specific transport protein for vitamin A in the blood, retinol binding protein 4 (RBP4) has been published. RBP4 is a novel adipokine that induces insulin resistance when body weight is gained. Secretory products from adipocytes partly link obesity with arterial hypertension, insulin resistance, inflammation, and atherosclerosis. A series of studies in mice have suggested that elevated RBP4 levels may play a causal role in the development of type 2 diabetes. However, studies in humans on this issue are controversial. Thus, careful evaluation of RBP4 in well-characterized human populations is crucial to define its precise role for development of type 2 diabetes.

Conclusions

Not all proteins shown to be relevant to diabetes in rodent models have proven their role in human diabetes. Whereas early studies clarified a potentially interesting role for RBP4 in glucose metabolism, further studies have suggested differences between rodent and human physiology. Moreover, results in humans have not been entirely consistent and it has been suggested that methodological differences, including the techniques used in the measurement of RBP4, as well as differences in the population studied, may account for the discrepancies [50].

The initial suggestion that RBP4 may be the link between obesity and insulin resistance is being challenged. The role of RBP4 in normal and abnormal physiology remains elusive. Further studies are clearly warranted to determine if RBP4 is a causative agent or a bystander.

References

1. Weber F. Biochemical mechanisms of vitamin A action. Proc Nutr Soc. 1983;42:31–41.
2. Bauernfeind JC. Carotenoid vitamin A precursors and analogs in foods and feeds. J Agric Food Chem. 1972;20:456–73.
3. Harrison EH. Mechanisms of digestion and absorption of dietary vitamin A. Annu Rev Nutr. 2005;25:87–103.
4. Bellovino D, Apreda M, Gragnoli S, Massimi M, Gaetani S. Vitamin A transport: in vitro models for the study of RBP secretion. Mol Aspects Med. 2003;24:411–20.
5. West KP. Vitamin A deficiency disorders in children and women. Food Nutr Bull. 2003;24(4 Suppl):S78–90.
6. Cantorna MT, Nashold FE, Hayes CE. Vitamin A deficiency results in a priming environment conducive for TH1 cell development. Eur J Immunol. 1995;25:1673–9.
7. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427–51.
8. Villalpando S, Montalvo-Velarde I, Zambrano N, García-Guerra A, Ramírez-Silva CI, Shamah-Levy T. Vitamins A, and C and folate status in Mexican children under 12 years and women 12-49 years: A probabilistic national survey. Salud Publica Mex. 2003;45:S508–19.
9. American Diabetes Association. Classification and diagnosis of diabetes. Diab Care. 2016;39 Supp 1:S13–22.
10. Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773e1779.
11. Krzyzanowska K, Zemany L, Krugluger W, et al. Serum concentrations of retinol-binding protein 4 in women with and without gestational diabetes. Diabetologia. 2008;51:1115–22.
12. Resende FB, De Lira LQ, Grilo EC, Lima MS, Dimenstein R. Gestational diabetes: a risk of puerperal hypovitaminosis A? An Acad Bras Cienc. 2015;87:463–70.

13. Sivaprasadarao A, Findlay JB. Structure-function studies on human retinol-binding protein using site-directed mutagenesis. Biochem J. 1994;300:437–42.
14. Klöting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, Fasshauer M, Schön MR, Stumvoll M, Blüher M, Kahn BB. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab. 2007;6:79–87.
15. Frey SK, Nagl B, Henze A, Raila J, Schlosser B, Berg T, Tepel M, Zidek W, Weickert MO, Pfeiffer AF, Schweigert FJ. Isoforms of retinol binding protein 4 (RBP4) are increased in chronic diseases of the kidney but not of the liver. Lipids Health Dis. 2008;7:29.
16. Bok D, Heller J. Transport of retinol from the blood to the retina: an autoradiographic study of the pigment epithelial cell surface receptor for plasma retinol-binding protein. Exp Eye Res. 1976;22:395–402.
17. Blaner WS. STRA6, a cell-surface receptor for retinol-binding protein: the plot thickens. Cell Metab. 2007;5:164–6.
18. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436:356–62.
19. Beetham R, Silver A, Dawnay A. Urinary albumin and retinol-binding protein in diabetes. Clin Chem. 1987;33:713.
20. Zovich DC, Orologa A, Okuno M, Kong LW, Talmage DA, Piantedosi R, Goodman DS, Blaner WS. Differentiation-dependent expression of retinoid- binding proteins in BFC-1 beta adipocytes. J Biol Chem. 1992;267:13884–9.
21. Shepherd PR, Kahn BB. Glucose transporters and insulin action–implications for insulin resistance and diabetes mellitus. N Engl J Med. 1999;341:248–57.
22. Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med. 2006;354:2552–63.
23. Polonsky KS. Retinol-binding protein 4, insulin resistance, and type 2 diabetes. N Engl J Med. 2006;354:2596–8.
24. Lee DC, Lee JW, Im JA. Association of serum retinol binding protein 4 and insulin resistance in apparently healthy adolescents. Metab, Clin Exp. 2007;56:327–31.
25. Gavi S, Stuart LM, Kelly P, Melendez MM, Mynarcik DC, Gelato MC. McNurlan MA: Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in nonobese subjects without type 2 diabetes. J Clin Endocrinol Metab. 2007;92:1886–90.
26. Balagopal P, Graham TE, Kahn BB, Altomare A, Funanage V, George D. Reduction of elevated serum retinol binding protein (RBP4) in obese children by lifestyle intervention: association with sub-clinical inflammation. J Clin Endocrinol Metab. 2007;92:1971–4.
27. Qi Q, Yu Z, Zhao F, Huang P, Hu FB, Franco OH, et al. Elevated retinolbinding protein 4 levels are associated with metabolic syndrome in Chinese people. J Clin Endocrinol Metab. 2007;92:4827–34.
28. Lewis JG, Shand BI, Elder PA, Scott RS. Plasma retinol-binding protein is unlikely to be a useful marker of insulin resistance. Diab Res Clin Pract. 2008;80:e13–5.
29. Promintzer M, Krebs M, Todoric J, Luger A, Bischof MG. Nowoty Pl. Insulin resistance is unrelated to circulating retinol binding protein and protein C inhibitor. J Clin Endocrinol Metab. 2007;92:4306–12.
30. Silha JV, Nyomba BL, Leslie WD, Murphy LJ. Ethnicity, insulin resistance, and inflammatory adipokines in women at high and low risk for vascular disease. Diabetes Care. 2007;30:286–91.
31. von Eynatten M, Lepper PM, Liu D, Lang K, Baumann M, Nawroth PP, Bierhaus A, Dugi KA, Heemann U, Allolio B, Humpert PM. Retinol-binding protein 4 is associated with components of the metabolic syndrome, but not with insulin resistance, in men with type 2 diabetes or coronary artery disease. Diabetologia. 2007;50:1930–7.
32. Lee DC, Lee JW, Im JA. Association of serum retinol binding protein 4 and insulin resistance in apparently healthy adolescents. Metab, Clin Exp. 2007;56:327–31.
33. Lewis JG, Shand BI, Frampton CM, Elder PA, Scott RS. Plasma retinol-binding protein is not a marker of insulin resistance in overweight subjects: a three year longitudinal study. Clin Biochem. 2008;41:1034–8.
34. Raila J, Henze A, Spranger J, Mo¨ hlig M, Pfeiffer AF, Schweigert JF. Microalbuminuria is a major determinant of elevated plasma retinol-binding protein 4 in type 2 diabetic patients. Kidney Int 2007;72:505–511.
35. Jaconi S, Rose K, Hughes GJ, Saurat JH, Siegenthaler G. Characterization of two post-translationally processed forms of human serum retinol-binding protein: altered ratios in chronic renal failure. J Lipid Res. 1995;36:1247–53.
36. Gavrilov V, Yermiahu T, Gorodischer R. Renal pathology and retinol status in multiple myeloma patients. Kidney Int. 2006;69:173–7.
37. Meigs JB, Panhuysen CI, Myers RH, Wilson PW, Cupples LA. A genome-wide scan for loci linked to plasma levels of glucose and HbA(1c) in a community-based sample of Caucasian pedigrees: the Framingham offspring study. Diabetes. 2002;51:833–40.

38. Duggirala R. Blangero, Almasy L, Dyer TD, Williams KL, Leach RJ, O'Connell P, Stern MP. Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. Am J Hum Genet. 1999;64:1127–40.
39. Munkhtulga L, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Erdenebulgan B, Zolzaya K, Lkhagvasuren T, Iwamoto S. Identification of a regulatory SNP in the retinol binding protein 4 gene associated with type 2 diabetes in Mongolia. Hum Genet. 2007;120:879–88.
40. Craig RL, Chu WS, Elbein SC. Retinol binding protein 4 as a candidate gene for type 2 diabetes and prediabetic intermediate traits. Mol Genet Metab. 2007;90:338–45.
41. Hu C, Jia W, Zhang R, Wang C, Lu J, Wu H, Fang Q, Ma X, Xiang K. Effect of RBP4 gene variants on circulating RBP4 concentration and type 2 diabetes in a Chinese population. Diabet Med. 2008;25:11–8.
42. Kovacs P, Geyer M, Berndt J, Klöting N, Graham TE, Böttcher Y, Enigk B, Tönjes A, Schleinitz D, Schön MR, Kahn BB, Blüher M, Stumvoll M. Effects of genetic variation in the human retinol binding protein-4 gene (RBP4) on insulin resistance and fat depot-specific mRNA expression. Diabetes. 2007;56:3095–100.
43. van Hoek M, Dehghan A, Zillikens MC, Hofman A, Witteman JC, Sijbrands EJ. An RBP4 promoter polymorphism increases risk of type 2 diabetes. Diabetologia. 2008;51:1423–8.
44. Lauenborg J, Grarup N, Damm P. Common type 2 diabetes risk gene variants associate with gestational diabetes. J Clin Endocrinol Metab. 2009;94:145–50.
45. Cho YM, Kim TH, Choi SH, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes in the Korean population. Diabetologia. 2009;52:253–61.
46. Ping F, Xiang HD, Li M, Li W, Liu JT, Nie M, Hui YC. Effects of variation in retinol binding protein 4 gene and adipose specific expression of gestational diabetes in Beijing, China. Diab Res Clin Pract. 2012;97:283–9.
47. Hiraoka M, Urschitz J, Sultan O, Ward K. A polymorphism in the retinol binding protein 4 gene is not associated with gestational diabetes mellitus in several different ethnic groups. Hawaii Med J. 2011;70:164–7.
48. Saucedo R, Zarate A, Basurto L, Hernandez M, Puello E, Mendoza-Lorenzo P, Ostrosky-Wegman P. RBP4 gene variants are associated with insulin resistance in women with previous gestational diabetes. Dis Markers 2014;2014:269208.
49. Hu S, Liu Q, Huang X, Tan H. Serum level and polymorphisms of retinol-binding protein-4 and risk for gestational diabetes mellitus: a meta-analysis. BMC Pregnancy Childbirth 2016;52.
50. Graham TE, Wason CJ, Bluher M, Kahn BB. Shortcomings in methodology complicate measurements of serum retinol binding protein (RBP4) in insulin-resistant human subjects. Diabetologia. 2007;50:814–23.

Chapter 13
Biomarkers of Metabolic and Cardiovascular Risk in Gestational Diabetes

Marloes Dekker Nitert, Leonie K. Callaway, H. David McIntyre and Helen L. Barrett

Key Points

- Early pregnancy biomarkers and metabolomics have yet to be clinically useful
- Abnormal maternal metabolism precedes and follows GDM
- Women with GDM are at increased risk of later cardiovascular disease and diabetes
- The increased risk of cardiovascular disease and diabetes is not only mediated by abnormalities in glucose and lipid metabolism, but also by inflammation and endothelial dysfunction

Keywords Gestational diabetes mellitus · Metabolism · Metabolomics · Cardiovascular disease · Type 2 diabetes mellitus

Introduction

Women who develop GDM enter pregnancy with abnormal metabolism, and continue to have metabolic dysfunction postpartum, predisposing them to cardiovascular disease and diabetes (Fig. 13.1). This metabolic dysfunction is not isolated to glucose and carbohydrate metabolism but includes lipid, amino acid, inflammatory, and intermediary aspects of metabolism. The early prediction of GDM prior to its onset would be clinically ideal, allowing the distribution of effort and resources to be used to target these high-risk women.

M.D. Nitert · H.L. Barrett (✉)
School of Medicine, The UQ Centre for Clinical Research, The University of Queensland, Herston Campus, Herston, QLD 4029, Australia
e-mail: h.barrett@uq.edu.au

M.D. Nitert
e-mail: m.dekker@uq.edu.au

L.K. Callaway · H.L. Barrett
Faculty of Medicine, School of Medicine, RBWH Clinical School, The UQ Centre for Clinical Research, The University of Queensland, Health Sciences Building, Herston Campus, Herston, QLD 4029, Australia
e-mail: l.callaway@uq.edu.au

H. David McIntyre
Faculty of Medicine, Mater Clinical School, The University of Queensland, South Brisbane, QLD 4101, Australia
e-mail: h.d.mcintyre@uq.edu.au

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_13

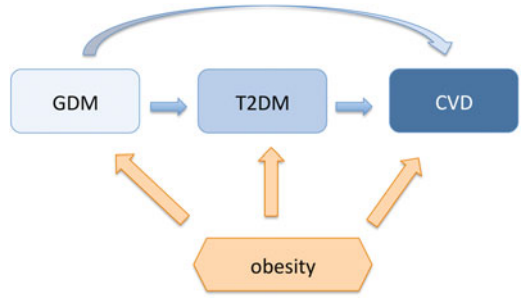


Fig. 13.1 Gestational diabetes mellitus, obesity are independent and intertwined predictors of later cardiovascular disease and type 2 diabetes mellitus

Early Pregnancy "Prediction" of GDM

Clues to the relationship of GDM and later cardiovascular and metabolic abnormalities may be found in the wide variety of inflammatory and metabolic markers which have been investigated in early pregnancy as potential "predictors" of a subsequent GDM diagnosis. The alterations in such markers in the early stages of pregnancy, often before the major pregnancy-related metabolic adaptations are present, suggest that women with GDM may frequently have (largely subclinical and undiagnosed) perturbations in these systems antedating pregnancy.

Placental proteins commonly assayed for the detection of other pregnancy complications such and aneuploidy have been evaluated in terms of their predictive value for GDM. Spencer et al. [1] have described low levels of PaPP-A (a trophoblast metalloprotease) in women who subsequently developed GDM. Lovati et al. [2] reported similar findings, but found that the subsequent predictive model developed using PaPP-A was of limited clinical utility, with 81% sensitivity for 51% specificity. By contrast, Husslein et al. reported no difference in PaPP-A levels between GDM women requiring insulin therapy (and thus presumably with more severe GDM) and controls. Another placental marker PlGF, which contributes to placental angiogenesis, has been noted to be elevated in women with subsequent GDM [3].

Sex hormone binding globulin (SHBG), low levels of which are marker of insulin resistance, has also been noted to be reduced in women with later GDM [3–5], but again this potential marker appears to lack sufficient discriminatory power [5] to be of clear clinical value. Reduced levels of adiponectin, an adipose tissue polypeptide which enhances insulin sensitivity have been widely reported in Type 2 diabetes [6] and are also found in women who subsequently develop GDM [7–9].

Markers of inflammation and endothelial dysfunction have also be evaluated as potential predictors of GDM. High sensitivity c reactive protein (hsCRP) is reportedly elevated in women who progress to GDM, though this association may be due to concurrent obesity [10]. Tumor necrosis factor alpha (TNFα) has also been noted to be elevated in women with subsequent GDM [11]. However, neither hsCRP nor TNFα appear to improve GDM prediction compared to a clinical risk model [12].

In summary, biochemical and hormonal changes associated later GDM are detectable in early pregnancy, but generally are not sufficiently predictive to be of clinical value. These changes do, however, serve to underline the fact that GDM is frequently preceded by detectable features of subclinical inflammation and insulin resistance and underline its longer term importance as a "warning flag" for future cardiovascular and metabolic disease.

Metabolomics and GDM

The study of intermediary aspects of metabolism (the "metabolome") has provided new information on early pregnancy metabolism in predicting later GDM, shown to be altered during GDM and in the infant born to a pregnancy complicated by GDM (Fig. 13.2).

Metabolomics have been suggested as one way to predict women who develop GDM later in the pregnancy. Early pregnancy studies suggest alterations in glucose, amino acids, lipoproteins [13]. One study of 48 women in the screening for pregnancy endpoints (SCOPE) study, in early pregnancy, identified itaconic acid as being higher in women who later developed GDM [14]. Itaconic acid may have a role in inflammation.

A systematic review in 2014 reported inconsistent results between studies in describing a particular maternal metabolomic profile in women with GDM [15]. It did report that the markers most consistently associated with GDM were asymmetric dimethylarginine (ADMA) and NEFAs. ADMA is thought to relate to endothelial dysfunction and elevated levels have been reported in various settings, including type 2 diabetes, atherosclerosis, and cardiovascular disease [16]. A large Norwegian cohort study of 823 women using H-NMR spectroscopy to examine the urinary metabolome could not reliably identify GDM cases [17]. More recent studies have suggested alterations in amino acids [18], lipid, and carbohydrate metabolism in women with GDM [19]. A case-control study from China examined hair samples taken at the time of oral glucose tolerance testing (OGTT) and examined the hair metabolome [20]. The hair metabolome in women with GDM showed higher levels of Adipic acid. Adipic acid is a food additive (amongst other manufacturing uses), and a marker of lipid peroxidation in diabetes [21].

Infants born to women with GDM show an altered metabolomics profile in cord blood at birth. In one study of 30 infants born to GDM and 40 control infants, all term deliveries, the infants born to GDM pregnancies had higher levels of pyruvate, histidine, alanine, valine, methionine, arginine, lysine, hypoxanthine, lipoprotein, and lipid than controls [22]. Another study of the infants of 142 women with GDM and 197 controls assessed meconium and urinary metabolome [23]. It identified changes in aspects of amino acid metabolism, purine metabolism, lipid metabolism, cocoa and tea metabolism, and nucleic acid metabolism. A combination of nine meconium metabolites had an AUC = 0.946 in the prediction of GDM.

At present, metabolomics studies, while showing some data of interest, frequently have failed to find a consistent metabolomics profile in women at risk of or with GDM, are not clinically useful and will require further exploration of large multiethnic cohorts.

GDM itself can be considered a "biomarker" in that it reveals underlying metabolic abnormalities. This underlying metabolism predisposes women with GDM to the later development of cardiovascular disease and diabetes mellitus.

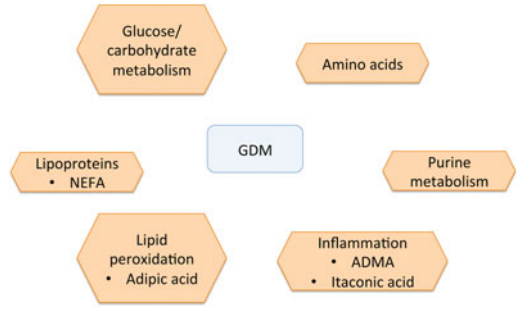


Fig. 13.2 Aspects of the metabolome identified as related to gestational diabetes mellitus

Cardiovascular Disease

Cardiovascular disease is the leading cause of death for women [24]. Pregnancy complications such as GDM can be predictors of later cardiovascular disease, and may be markers to identify those women who should be monitored more closely and receive early intervention to reduce cardiovascular disease risks. A recent narrative review indicated that increased glucose levels and diabetes mellitus are cardiovascular risk factors. High-risk GDM women also had alterations in risk factors associated with cardiovascular disease such as abnormal lipid profiles, increased waist circumference, increased insulin resistance and increased circulating insulin concentration, elevated hs-CRP and a greater carotid intima-media thickness postpartum [25]. In fact, women with GDM who had a higher 1 h glucose value at an 75 g OGTT during pregnancy or postpartum demonstrated increased risk of cardiovascular disease, indicating that peak glucose levels are important predictors for future cardiovascular disease [25]. Furthermore, women with GDM had decreased cardiac output, decreased stroke volume, and increased peripheral vascular resistance at 1 year postpartum [25], predisposing these women to cardiovascular disease. Increased arterial stiffness, perhaps due to greater exposure to advanced glycation end products, has also been noted in women after a pregnancy complicated by GDM [25].

GDM is associated with later cardiovascular risk (Table 13.1). Some but not all of this risk is mediated through the postpartum development of type 2 diabetes and by coexisting obesity. A Canadian cohort study of 8191 women with GDM and 81,262, followed for a median 11.5 years showed a Hazard ratio for CVD events of 1.71 (95% CI 1.08–2.69), which was attenuated by adjustment for the postpartum development of type 2 diabetes [26]. In contrast, a recent prospective

Table 13.1 Registry studies examining cardiovascular outcomes following gestational diabetes mellitus

Country	Numbers	Source	Length of follow-up postpartum	CVD outcomes
[26] Canada	• 8191 GDM, 81,262 control	Administrative databases in Ontario	11.5 years	HR CVD events 1.71 (95% CI 1.08–2.69)
[27] Netherlands	• 1089 GDM • 15,560 control	European prospective investigation into Cancer and Nutrition-NL study	~28 years post first pregnancy	No change in CVD risk related to previous GDM
[28] Canada	• 1399 Overweight with GDM • 7332 GDM only, 17,587 overweight only • 213,765 normoglycemic, normal weight	Alberta perinatal health program	5.3 years	aHR for cardiovascular outcomes GDM and overweight aHR 2.1 (1.1, 3.5) GDM only aHR 1.4 (1.0, 1.9) Overweight only aHR 1.5 (1.2, 1.8)
[29] Sweden	2639 women with cardiovascular events	National Swedish register data	9.1 years	aOR for CVD 1.51 (95% CI 1.07–2.14) in women with previous GDM
[30] France	• 62,958 GDM • >1.5 million deliveries	French medico-administrative database	7 years	Risk of cardiovascular disease aOR 1.25 (1.09–1.43) Increased risks of angina pectoris aOR = 1.68 (1.29–2.20) Myocardial infarction aOR = 1.92 (1.36–2.71) Hypertension aOR = 2.72 (2.58–2.88)

cohort study from The Netherlands including 1089 women with GDM and 15,560 controls, reported that in women with GDM, there was no change in the risk of cardiovascular disease even though the risk of type 2 diabetes was increased by 3.68 fold [27]. However, the lack of association with cardiovascular disease could be due to the relatively small number of women with GDM in this cohort and the relatively short follow-up time between the diagnosis of type 2 diabetes and CVD [27]. In another Canadian cohort study with a median follow-up time of 5.3 years, women who were overweight (defined as having a prepregnancy weight of >91 kg rather than by BMI) and had GDM had fivefold increased incidence of future hypertension and a threefold increased incidence of future cardiovascular disease compared with normal weight, non GDM women [28]. Women who were either overweight or had GDM had a 3 fold risk of future hypertension and a 1.5–2 fold increased risk of cardiovascular disease [28]. These results indicate that both overweight and GDM incur increased risks that compound when cooccurring.

A similar registry-based case-control study from Sweden examining 2639 women with cardiovascular events, reported adjusted odds (aOR) for cardiovascular disease in women with previous GDM of 1.51 (95% CI 1.07–2.14). In this study, diabetes after pregnancy had a strong association with CVD [aOR 4.80 (95% CI 3.23–7.13)]. For the cohort as a whole, adjusting for diabetes after pregnancy removed the association between GDM and CVD. For women with BMI >25 kg/m^2, the association between GDM and CVD was aOR 2.39 (95% CI 1.39–4.10), $P = 0.002$ and adjusting for diabetes after pregnancy attenuated the association of GDM with CVD only slightly to 1.99 (95% CI 1.13–3.52) [29].

A nationwide database study in France of >1.5 million deliveries including 62,958 women with GDM, followed up for 7 years postpartum, and adjusting for age, diabetes mellitus, and pregnancy hypertension, showed GDM was significantly associated with future risk of cardiovascular disease [aOR 1.25 (1.09–1.43)], and with increased risks of angina pectoris [aOR = 1.68 (1.29–2.20)], myocardial infarction [aOR = 1.92 (1.36–2.71)], and hypertension [aOR = 2.72 (2.58–2.88)] but not stroke [30]. Maternal overweight and obesity, as well as the postpartum development of diabetes, influence but do not entirely explain the later cardiovascular risk associated with GDM. There is evidence of abnormal endothelial function, vascular responsiveness, and early atherosclerosis present during pregnancies complicated by GDM and in the early postpartum period.

Endothelial Dysfunction

Endothelial dysfunction and loss of vascular responsiveness predisposes to cardiovascular disease and atherosclerosis (Table 13.2). Endothelial dysfunction also is present in type 2 diabetes and may contribute to dysfunctional glucose disposal through the loss of insulin's vasoactive properties. Dysfunctional endothelium also displays increased expression of adhesion molecules which may maintain inflammation and further promote an atherogenic milieu [31].

Table 13.2 Endothelial dysfunction parameters changes in women with gestational diabetes mellitus during pregnancy and postpartum

	During pregnancy	Postpartum
Pulse wave velocity	[32]	[38, 39]
Central SBP	[32]	
Brachial artery dilation	Unchanged [33]	
Forearm skin blood flow	[34]	
Skin microvascular reactivity	Unchanged [36]	
Flow-mediated dilation		[37]

SBP systolic blood pressure

Endothelial Dysfunction in GDM

In early pregnancy, there is some evidence of increased arterial stiffness in those women who later develop GDM. One cohort of 105 women who later developed GDM were compared to 6736 non-GDM controls and demonstrated an increase in pulse wave velocity (1.04 MoM, interquartile range (IQR) 0.93–1.15 vs. 1.00 MoM, IQR 0.90–1.12; $p = 0.013$) and central systolic blood pressure (1.03 MoM, IQR 0.98–1.14 vs. 1.00 MoM, IQR 0.94–1.08; $p < 0.0001$) [32]. In a cross-sectional study, 42 women with preeclampsia, 19 women with GDM and 19 normotensive control women were assessed by flow-mediated dilation. The mean values of brachial artery dilation were similar between women with preeclampsia and gestational diabetes, and significantly lower than the control group [preeclampsia (FMD = 5.36 ± 4.61%), gestational diabetes (FMD = 9.18 ± 5.98%), and control (FMD = 17.55 ± 8.35%)] [33]. A case-control study of 28 women with GDM and 24 control women in the third trimester found reduced forearm skin blood flow in response to acetylcholine (344.59 ± 57.791 vs. 176.38 ± 108.52, $P < 0.05$) [34]. Abnormal endothelial function has also been demonstrated in women with impaired glucose tolerance in pregnancy, with brachial artery flow-mediated dilation reduced in 10 women with impaired glucose tolerance and 13 women with GDM compared to control women in the third trimester (7.6 ± 1.1%) in the IGT group and 4.1 ± 0.9% in the GDM group vs. 10.9 ± 1.1% in control subjects, $P < 0.04$ and $P < 0.0001$ [35]. In contrast, an examination of skin microvascular reactivity by laser Doppler fluviometry in women at 33 weeks showed no difference between women with and without GDM [36].

Endothelial Dysfunction After GDM

The relationship between GDM and endothelial dysfunction continues postpartum. One case-control study of 33 women with GDM and 19 control women (where the women with previous GDM currently had normal glucose tolerance) reported that flow-mediated dilation was reduced in both the obese and non-obese women with previous GDM compared to controls (1.6 ± 3.7% in the non-obese GDM group and 1.6 ± 2.5% in the obese GDM group versus 10.3 ± 4.4% in control subjects, $P < 0.001$) [37].

A sub-study of Chinese women in the HAPO cohort, followed up a median of 6 years postpartum showed a higher augmentation index (22.1 ± 8.3 vs. 18.9 ± 8.5%, $p < 0.001$), and pulse wave velocity (6.8 ± 1.0 vs. 6.6 ± 0.8, $p = 0.03$) in women who had a history of GDM, suggesting an increased risk of atherosclerosis [38]. This has been echoed in a prospective cohort study of 300 women, showing that women who met WHO GDM criteria (but not those who met IADPSG criteria) had higher pulse wave velocity [6.7 m/s (95% CI 6.4–7.3) c/w 6.6 (6.1–7.1)], and higher triglyceride/HDL ratio [0.52 (0.42–0.76) c/w 0.45 (0.36–0.63)] than whose without GDM at 5 years postdelivery [39].

Early Atherosclerosis

A recent meta-analysis showed that subclinical atherosclerosis, as defined by an increased thickness of the carotid intima media, was increased in women with GDM and that this was independent of maternal age and whether or not the measurement was performed in or after pregnancy [40]. However, BMI was positively correlated with carotid intima-media thickness [40] indicating that there is an interaction between obesity and GDM. Common carotid artery intima-media thickness

(CIMT) is increased in GDM, with 30 women with GDM compared to 40 control, (0.582 ± 0.066 mm vs. 0.543 ± 0.049 mm, $P = 0.006$) [41] Furthermore, the circulating levels of the adipocytokine apelin are decreased by 40% in women on average 3 years post-GDM. Apelin also showed a negative correlation with carotid intima-media thickness, circulating IL-6 levels and fasting, and post-load glucose levels [42].

Atherosclerosis is mediated by cellular adhesion molecules. In one study of women with previous GDM, levels of adhesion markers (sICAM-1, sVCAM-1, and sE-selectin) were increased compared to women without prior GDM [31]. This effect was independent of their current insulin sensitivity status. While there was no increase in the levels of these adhesion markers over up to ten years of follow-up, they did increase in those women who progressed to overt type 2 diabetes [31]. The levels of adhesion markers were negatively correlated to measures of insulin sensitivity, and therefore, may be of use as biomarkers for both cardiovascular and metabolic disease in women after GDM [31]. However, another study reported no differences in mean levels of adhesion molecules in women post GDM [43]. However, ICAM levels were reportedly positively correlated with fasting glycaemia, 2-h glycaemia in OGTT and HOMA index [43] indicating that endothelial dysfunction may be more pronounced in women with decreased insulin sensitivity which is more common with prior GDM. Other factors that may contribute to endothelial dysfunction are reduced bioactivity of the vascular nitric oxide system, higher concentrations of the endothelial adhesion molecules VCAM-1 and E-selectin, higher circulating triglycerides, proinsulin, and PAI-1 (tissue plasminogen activator) levels [25].

Metabolic Outcomes After GDM

In women who have had GDM, the risk for developing type 2 diabetes is increased by 7.4 fold compared to women with normoglycemic pregnancies [44]. This appears to be independent of the number of pregnancies affected by GDM since recurrence of GDM does not increase the metabolic or cardiovascular risk any further [45]. This indicates that pregnancy unmasks predispositions rather than causes acute damage.

In GDM, the physiological increase in insulin resistance of pregnancy is not fully compensated by increased insulin secretion. GDM therefore can identify women with preexisting lower beta cell secretory capacity which persists after the completion of pregnancy. Chronic beta-cell insufficiency may lead to the development of type 2 diabetes especially in the setting of obesity. A Norwegian cohort study reported decreased beta cell function at 5 years postpartum in women who had GDM even after adjustment for maternal age, smoking, family history of diabetes, follow-up time, parity and BMI [46]. The decrease in beta cell function was correlated with an increase in visceral adipose tissue mass in women with GDM [46], suggesting that increased visceral fat mass specifically may contribute to the higher risk for metabolic disease in women with GDM. Visceral adipose tissue is known to be more metabolically active and secrete more inflammatory mediators than subcutaneous adipose tissue.

There are additional risk factors for the future development of type 2 diabetes in women with GDM. These include insulin requirement during pregnancy, maternal obesity, family history of diabetes, and ethnicity. Since the risk factors for GDM and type 2 diabetes overlap to a great extent, this could indicate that there is a common pathology underlying their development. In fact, the genetic predisposition profiles for GDM and type 2 diabetes are remarkably similar [47]. A diagnosis of GDM should therefore give rise to increased surveillance of the affected woman for the development of future diabetes especially in order to reduce the risks of diabetes-associated cardiovascular and renal complications.

Ethnicity

A number of studies have evaluated the role of ethnicity in determining the risk of (type 2) diabetes after a pregnancy complicated by GDM [48, 49]. Chinese and Caucasian ethnicity confer the lowest risks whereas black or South Asian women have a twofold higher risk of developing type 2 diabetes [48, 49]. The cumulative incidence of diabetes in South Asian women 12.5 years after the index pregnancy was 50% [48]. However compared to women with normoglycemic pregnancies, the risk of developing diabetes was increased by 10-, 10- and 13-fold for Chinese, South Asian and Caucasian women, respectively [48]. These results indicate that GDM may have differential effects on the risk for later diabetes in different ethnic groups which may be due to differences in pregnancy physiology or to differences in lifestyle, dietary or cultural factors between ethnic groups.

Prediction Tool

Recently, a prediction tool was proposed for the stratification of women into different risk categories for the development of type 2 diabetes [50]. This model was developed based on a 257 islet autoantibody-negative women from a German cohort study with an average follow-up of women of up to 20 years and 110 women (42.8%) developing postpartum diabetes during follow-up. This model uses a combination of four factors to calculate a risk score: early pregnancy BMI, insulin treatment for GDM, family history of diabetes, and lactation duration.

The risk score is calculated as follows: Risk score = 5*early pregnancy BMI(kg/m^2) + 132 (GDM treated with insulin; else 0) + 44 (if family history of diabetes; else 0)—35 (if breastfed baby; else 0). The risk scores were then divided into four equally spaced risk categories with estimation of 13% risk for the lowest category (score <140); 31% for scores between 140 and 220); 60% for scores between 221 and 300; and 90% for the very high-risk category with scores >300. This risk score may help in allocating follow-up resources to the group of women at very high risk of developing type 2 diabetes after a diagnosis of GDM.

A previous study in Australia identified women at risk for developing type 2 diabetes when they had four or more elevations in maternal BMI, fasting glucose, insulin, triglycerides, HDL cholesterol, and systolic blood pressure [51]. Genetic risk scores have also been calculated which in conjunction with metabolic parameters such as family history, prepregnancy BMI, blood pressure, fasting glucose, and insulin and age slightly improved the prediction of developing type 2 diabetes as well [52]. It is not clear whether or not this slight improvement justifies the costs.

The level of glucose abnormality during pregnancy is also associated with risk for postpartum diabetes. The HAPO study showed that in pregnancy, there was a continuous relationship between glucose values and adverse perinatal outcomes [53]. A recent study from Finland identified an increased risk for postpartum diabetes in women with one abnormal glucose value on the diagnosing OGTT at 28 weeks gestation by with an incidence of 3.8% at >10 years postpartum, but a greater increased risk for women with >1 abnormal glucose value with a 25% incidence at >10 years postpartum [54]. This equated to an approximately 73 fold increase in the risk for developing type 2 diabetes in women with >1 abnormal glucose value on the 28 week OGTT.

Short-Term Measurements

Most studies of short-term measurements investigate women in the first year after delivery. Women who had GDM have higher insulin and glucose levels than women with normoglycemic pregnancies postpartum [43, 54, 55]. They reportedly show a lower disposition index and Matsuda index of insulin sensitivity but no difference in HOMA-IR in an OGTT at approximately 9 months postdelivery [55]. However, total fat mass, visceral fat volume, and hepatic fat content was not different postpartum between women with or without GDM [55]. Nonesterified fatty acids are important biomarkers for type 2 diabetes and metabolic syndrome [55]. In the fasting state, NEFAs in the circulation mainly reflect storage in adipose tissue. In women with GDM, there were no changes in total NEFA concentrations although there were a slight decrease in short chain fatty acids and slightly higher proportions of linoleic acid and total omega-6 nonesterified fatty acids [55].

Further, the type 2 diabetes hepatic biomarker fetuin-A as well as the adipokine leptin showed increased levels in postpartum women with GDM [55, 56]. Fetuin-A is involved in inflammatory signaling. A greater proportion of women who had GDM have been reported to have hypo-HDL cholesterol values [43]. Levels of the oxidative stress marker catalase were increased in women post GDM and triglyceride levels were positively correlated with glutathione transferase activity levels [43]. Furthermore, HDL cholesterol levels were positively correlated with superoxide dismutase and glutathione peroxidase activity but negatively correlated with glutathione transferase activity [43].

Protective Factors: Breastfeeding

Women with GDM who breastfeed have lower fasting glucose and insulin levels, improved HDL cholesterol levels at 3–4 months postpartum [57]. In long-term follow-up (20 year) of the CARDIA (Coronary Artery Risk Development in Young Adults) cohort in the USA, duration of breastfeeding was protective for developing metabolic syndrome in women with and without GDM [58]. However, the protective effect in women with GDM increased with increasing breastfeeding length whereas in women without GDM, the protective effect was reached when breastfeeding length exceeded 1 month [58]. The effects of breastfeeding have been hypothesized to be due to increased weight loss, altered body composition and adipose tissue deposition, or altered circulating lipid profiles [57] although definitive evidence for any or all of these hypotheses is lacking. Other studies have confirmed the protective effects of breastfeeding for type 2 diabetes mellitus, hyperlipidemia, hypertension and cardiovascular disease in women with GDM if cumulative breastfeeding time exceeded 12 months over a woman's lifetime [25] although these benefits were limited to Caucasian women only.

Breastfeeding and the Infant

Macrosomia and neonatal hypoglycemia are more common in offspring of women with GDM. Early breastfeeding has been associated with lower rates of borderline neonatal hypoglycemia and with higher overall blood glucose levels [59]. Breastfed infants have lower rates of obesity in general [59], whether this is true for breastfed infants of women with GDM is not clear.

Protective Factors: Lifestyle Intervention

A recent small RCT randomizing GDM women to either an 3 month exercise/diet intervention or standard care after delivery showed that there was a significant higher weight loss in the intervention group, leading to lower BMI [60]. Further, there was a significant reduction in hip and waist circumference but no significant difference in % body fat, fasting glucose and fasting insulin in the intervention group [60]. However, the authors reported that recruitment to the study was hampered by women citing lack of time and difficulties of making changes for the whole family [60]. This suggests that while improving diet and exercise has positive effects on predictors for type 2 diabetes, implementation in the at-risk population as a whole may not be feasible.

Protective Factors: Pharmacological Intervention

Some studies have shown that treatment with metformin or pioglitazone for women post GDM may decrease the progression to type 2 diabetes and cardiovascular disease [25].

Recommendations and Guidelines

There is metabolic risk that precedes and follows the brief period of GDM encountered during pregnancy. GDM is a strong predictor for lifelong health of mother and infant, and both should be managed clinically with this in mind. Future areas for exploration involve prediction tools for GDM diagnosis and for long-term complication risk.

Conclusions

Women who develop GDM are to some extent identifiable in early pregnancy, but there is no single best method for this. Further exploration of the impacts of ethnicity and diet, as well as newer technology allowing the analysis of the metabolome may lead to further insight in this area. GDM and the continuation of abnormal metabolism and excess inflammation in the postpartum period underlie the links seen between GDM and later cardiovascular and metabolic risk.

References

1. Spencer K, Cowans NJ. The association between gestational diabetes mellitus and first trimester aneuploidy screening markers. Ann Clin Biochem. 2013;50(Pt 6):603–10.
2. Lovati E, Beneventi F, Simonetta M, Laneri M, Quarleri L, Scudeller L, et al. Gestational diabetes mellitus: including serum pregnancy-associated plasma protein-A testing in the clinical management of primiparous women? A case-control study. Diabetes Res Clin Pract. 2013;100(3):340–7.
3. Eleftheriades M, Papastefanou I, Lambrinoudaki I, Kappou D, Lavranos D, Akalestos A, et al. Elevated placental growth factor concentrations at 11-14 weeks of gestation to predict gestational diabetes mellitus. Metabolism. 2014;63(11):1419–25.

4. Caglar GS, Ozdemir ED, Cengiz SD, Demirtas S. Sex-hormone-binding globulin early in pregnancy for the prediction of severe gestational diabetes mellitus and related complications. J Obstet Gynaecol Res. 2012; 38(11):1286–93.
5. Sweeting A, Park F, Hyett J. The first trimester: prediction and prevention of the great obstetrical syndromes. Best Pract Res Clin Obstet Gynaecol. 2015;29(2):183–93.
6. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302(2):179–88.
7. Williams MA, Qiu C, Muy-Rivera M, Vadachkoria S, Song T, Luthy DA. Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. J Clin Endocrinol Metab. 2004;89(5):2306–11.
8. Lain KY, Daftary AR, Ness RB, Roberts JM. First trimester adipocytokine concentrations and risk of developing gestational diabetes later in pregnancy. Clin Endocrinol. 2008;69(3):407–11.
9. Nanda S, Savvidou M, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks. Prenat Diagn. 2011;31(2):135–41.
10. Berggren EK, Roeder HA, Boggess KA, Moss K, Offenbacher S, Campbell E, et al. First-trimester maternal serum C-reactive protein as a predictor of third-trimester impaired glucose tolerance. Reprod Sci. 2015;22(1):90–3.
11. Bo S, Signorile A, Menato G, Gambino R, Bardelli C, Gallo ML, et al. C-reactive protein and tumor necrosis factor-alpha in gestational hyperglycemia. J Endocrinol Invest. 2005;28(9):779–86.
12. Syngelaki A, Visser GH, Krithinakis K, Wright A, Nicolaides KH. First trimester screening for gestational diabetes mellitus by maternal factors and markers of inflammation. Metabolism. 2016;65(3):131–7.
13. Pinto J, Almeida LM, Martins AS, Duarte D, Barros AS, Galhano E, et al. Prediction of gestational diabetes through NMR metabolomics of maternal blood. J Proteome Res. 2015;14(6):2696–706.
14. de Seymour JV, Conlon CA, Sulek K, Villas Boas SG, McCowan LM, Kenny LC, et al. Early pregnancy metabolite profiling discovers a potential biomarker for the subsequent development of gestational diabetes mellitus. Acta Diabetol. 2014;51(5):887–90.
15. Huynh J, Xiong G, Bentley-Lewis R. A systematic review of metabolite profiling in gestational diabetes mellitus. Diabetologia. 2014;57(12):2453–64.
16. Assar ME, Angulo J, Santos-Ruiz M, de Adana JC, Pindado ML, Sanchez-Ferrer A, et al. ADMA elevation and arginase up-regulation contribute to endothelial dysfunction related to insulin resistance in rats and morbid obese humans. J Physiol. 2016.
17. Sachse D, Sletner L, Morkrid K, Jenum AK, Birkeland KI, Rise F, et al. Metabolic changes in urine during and after pregnancy in a large, multiethnic population-based cohort study of gestational diabetes. PLoS ONE. 2012;7 (12):e52399.
18. Lehmann R, Friedrich T, Krebiehl G, Sonntag D, Haring HU, Fritsche A, et al. Metabolic profiles during an oral glucose tolerance test in pregnant women with and without gestational diabetes. Exp Clin Endocrinol Diab. 2015;123(7):483–38.
19. Liu T, Li J, Xu F, Wang M, Ding S, Xu H, et al. Comprehensive analysis of serum metabolites in gestational diabetes mellitus by UPLC/Q-TOF-MS. Anal Bioanal Chem. 2016;408(4):1125–35.
20. He X, de Seymour JV, Sulek K, Qi H, Zhang H, Han TL, et al. Maternal hair metabolome analysis identifies a potential marker of lipid peroxidation in gestational diabetes mellitus. Acta Diabetol. 2016;53(1):119–22.
21. Inouye M, Mio T, Sumino K. Dicarboxylic acids as markers of fatty acid peroxidation in diabetes. Atherosclerosis. 2000;148(1):197–202.
22. Dani C, Bresci C, Berti E, Ottanelli S, Mello G, Mecacci F, et al. Metabolomic profile of term infants of gestational diabetic mothers. J Matern Fetal Neonatal Med. 2014;27(6):537–42.
23. Peng S, Zhang J, Liu L, Zhang X, Huang Q, Alamdar A, et al. Newborn meconium and urinary metabolome response to maternal gestational diabetes mellitus: a preliminary case-control study. J Proteome Res. 2015;14 (4):1799–809.
24. Westerman S, Wenger NK. Women and heart disease, the underrecognized burden: sex differences, biases, and unmet clinical and research challenges. Clin Sci (Lond). 2016;130(8):551–63.
25. Harreiter J, Dovjak G, Kautzky-Willer A. Gestational diabetes mellitus and cardiovascular risk after pregnancy. Women's Health. 2013;10(1):91–108.
26. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008;31(8):1668–9.
27. Heida KY, Franx A, van Rijn BB, Eijkemans MJC, Boer JMA, Verschuren MWM, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. Hypertension. 2015.
28. Kaul P, Savu A, Nerenberg KA, Donovan LE, Chik CL, Ryan EA, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabet Med. 2015;32(2):164–73.

29. Fadl H, Magnuson A, Ostlund I, Montgomery S, Hanson U, Schwarcz E. Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case-control study. BJOG. 2014;121(12):1530–6.
30. Goueslard K, Cottenet J, Mariet AS, Giroud M, Cottin Y, Petit JM, et al. Early cardiovascular events in women with a history of gestational diabetes mellitus. Cardiovasc Diabetol. 2016;15(1):15.
31. Gobl CS, Bozkurt L, Yarragudi R, Prikoszovich T, Tura A, Pacini G, et al. Biomarkers of endothelial dysfunction in relation to impaired carbohydrate metabolism following pregnancy with gestational diabetes mellitus. Cardiovasc Diabetol. 2014;13:138.
32. Khalil A, Garcia-Mandujano R, Chiriac R, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11–13 weeks' gestation in gestational diabetes mellitus. Fetal Diagn Ther. 2012;31(4):216–20.
33. Guimaraes MF, Brandao AH, Rezende CA, Cabral AC, Brum AP, Leite HV, et al. Assessment of endothelial function in pregnant women with preeclampsia and gestational diabetes mellitus by flow-mediated dilation of brachial artery. Arch Gynecol Obstet. 2014;290(3):441–7.
34. Mrizak I, Arfa A, Fekih M, Debbabi H, Bouslema A, Boumaiza I, et al. Inflammation and impaired endothelium-dependant vasodilatation in non obese women with gestational diabetes mellitus: preliminary results. Lipids Health Dis. 2013;12:93.
35. Paradisi G, Biaggi A, Ferrazzani S, De Carolis S, Caruso A. Abnormal carbohydrate metabolism during pregnancy: association with endothelial dysfunction. Diab Care. 2002;25(3):560–4.
36. Pontes IE, Afra KF, Silva JR Jr, Borges PS, Clough GF, Alves JG. Microvascular reactivity in women with gestational diabetes mellitus studied during pregnancy. Diabetol Metab Syndr. 2015;7:27.
37. Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, et al. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. Diab Care. 1998;21 (12):2111–5.
38. Tam WH, Ma RC, Chan JC, Lao TT, Chan MH, Li CY. PP103. Arterial stiffness in women with previous GDM—A follow up of Chinese HAPO study cohort. Pregnancy Hypertens. 2012;2(3):295.
39. Lekva T, Bollerslev J, Norwitz ER, Aukrust P, Henriksen T, Ueland T. Aortic stiffness and cardiovascular risk in women with previous gestational diabetes mellitus. PLoS ONE. 2015;10(8):e0136892.
40. Li J-W, He S-Y, Liu P, Luo L, Zhao L, Xiao Y-B. Association of gestational diabetes mellitus (GDM) with subclinical atherosclerosis: a systemic review and meta-analysis. BMC Cardiovasc Dis. 2014;14(1):132.
41. Tarim E, Yigit F, Kilicdag E, Bagis T, Demircan S, Simsek E, et al. Early onset of subclinical atherosclerosis in women with gestational diabetes mellitus. Ultrasound Obstet Gynecol (the official journal of the International Society of Ultrasound in Obstetrics and Gynecology). 2006;27(2):177–82.
42. Akinci B, Celtik A, Tunali S, Genc S, Yuksel F, Secil M, et al. Circulating apelin levels are associated with cardiometabolic risk factors in women with previous gestational diabetes. Arch Gynecol Obstet. 2014;289(4):787–93.
43. Roca-Rodriguez MM, Lopez-Tinoco C, Murri M, Fernandez-Deudero A, Garcia-Palacios MV, Garcia-Valero MA, et al. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus. J Endocrinol Invest. 2014;37(6):503–9.
44. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773–9.
45. Winhofer Y, Tura A, Prikoszovich T, Winzer C, Schneider B, Pacini G, et al. The impact of recurrent gestational diabetes on maternal metabolic and cardiovascular risk factors. Eur J Clin Invest. 2013;43(2):190–7.
46. Lekva T, Bollerslev J, Godang K, Roland MCP, Friis CM, Voldner N, et al. Œ $\leq$ -cell dysfunction in women with previous gestational diabetes is associated with visceral adipose tissue distribution. Eur J Endocrinol. 2015;173 (1):63–70.
47. Mao H, Li Q, Gao S. Meta-analysis of the relationship between common type 2 diabetes risk gene variants with gestational diabetes mellitus. PLoS ONE. 2012;7(9):e45882.
48. Mukerji G, Chiu M, Shah BR. Impact of gestational diabetes on the risk of diabetes following pregnancy among Chinese and South Asian women. Diabetologia. 2012;55(8):2148–53.
49. Xiang AH, Li BH, Black MH, Sacks DA, Buchanan TA, Jacobsen SJ, et al. Racial and ethnic disparities in diabetes risk after gestational diabetes mellitus. Diabetologia. 2011;54(12):3016–21.
50. Kohler M, Ziegler AG, Beyerlein A. Development of a simple tool to predict the risk of postpartum diabetes in women with gestational diabetes mellitus. Acta Diabetol. 2015;1–5.
51. Barden A, Singh R, Walters B, Phillips M, Beilin LJ. A simple scoring method using cardiometabolic risk measurements in pregnancy to determine 10-year risk of type 2 diabetes in women with gestational diabetes. Nutr Diab. 2013;3(6):e72.
52. Kwak S, Choi S, Kim K, Jung H, Cho Y, Lim S, et al. Prediction of type 2 diabetes in women with a history of gestational diabetes using a genetic risk score. Diabetologia. 2013;56(12):2556–63.
53. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. Pediatrics. 2010;126(6):e1545–52.

54. Hakkarainen H, Huopio H, Cederberg H, Paakkonen M, Voutilainen R, Heinonen S. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. Gynecol Endocrinol. 2015;31(7):573–7.
55. Fugmann M, Uhl O, Hellmuth C, Hetterich H, Kammer NN, Ferrari U, et al. Differences in the serum nonesterified fatty acid profile of young women associated with a recent history of gestational diabetes and overweight/obesity. PLoS ONE. 2015;10(5):e0128001.
56. Rottenkolber M, Ferrari U, Holland L, Aertsen S, Kammer NN, Hetterich H, et al. The diabetes risk phenotype of young women with recent gestational diabetes. J Clin Endocrinol Metab. 2015;100(6):E910–8.
57. Gunderson EP, Kim C, Quesenberry CP Jr, Marcovina S, Walton D, Azevedo RA, et al. Lactation intensity and fasting plasma lipids, lipoproteins, non-esterified free fatty acids, leptin and adiponectin in postpartum women with recent gestational diabetes mellitus: the SWIFT cohort. Metabolism. 2014;63(7):941–50.
58. Gunderson EP, Jacobs DR, Chiang V, Lewis CE, Feng J, Quesenberry CP, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes. 2010;59(2):495–504.
59. Trout K, Averbuch T, Barowski M. Promoting breastfeeding among obese women and women with gestational diabetes mellitus. Curr Diab Rep. 2011;11(1):7–12.
60. Peacock AS, Bogossian FE, Wilkinson SA, Gibbons KS, Kim C, McIntyre HD. A randomised controlled trial to delay or prevent type 2 diabetes after gestational diabetes: walking for exercise and nutrition to prevent diabetes for you. Int J Endocrinol. 2015;2015:8.

Chapter 14
Fish Oil and Cardiac Akt/mTOR-Mediated Insulin Resistance in Infants with Maternal Diabetes

Akio Nakamura and Ritsuko Kawaharada

Key Points

- Infants of diabetic mothers (IDMs) have circulation-related abnormalities.
- We constructed an animal model exhibiting high blood glucose levels during pregnancy.
- IDMs exhibited abnormalities in cardiac Akt/mammalian target of rapamycin (mTOR)-mediated insulin signalling, which was improved by a fish oil-rich maternal diet.
- Eicosapentaenoic acid (EPA) in fish oil may improve impaired signalling in cardiomyocytes of IDMs.
- Molecular mechanisms underlying EPA-mediated improvement of Akt/mTOR-mediated insulin signalling was identified in cardiac muscles.
- Our findings provide evidence for supplementation of dietary management of pregnant diabetic women with EPA nutritional therapy.

Keywords Fish oil · Omega-3 polyunsaturated fatty acids · Eicosapentaenoic acid · Heart · Cardiac muscle · Akt · Insulin signalling · Infant of diabetic mother · Nutrition · Maternal diabetes

Abbreviations

IDMs	Infants of diabetic mothers
mTOR	Mammalian target of rapamycin
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
PUFAs	Polyunsaturated fatty acids
PA	Palmitic acid
IRS	Insulin receptor substrate
GLUT4	Glucose transporter type 4
MAPK	Mitogen-activated protein kinase
JNK	C-Jun N-terminal kinase
ET-1	Endothelin-1
GPCR	G protein-coupled receptor

A. Nakamura (✉)
Department of Molecular Pharmacology and Oncology, School of Medicine,
Gunma University, 3-39-22 Showa-Machi, Maebashi, Gunma 371-8511, Japan
e-mail: gacho@gunma-u.ac.jp

R. Kawaharada
Department of Nutrition, Faculty of Health and Welfare, Takasaki University of Health and Welfare,
37-1 Nakaorui-Machi, Takasaki, Gunma 370-0033, Japan
e-mail: nasu@takasaki-u.ac.jp

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_14

HUVEC	Shuman umbilical vein endothelial cells
TGF-β1	Transforming growth factor β1
NF-κB	Nuclear factor κB
TNF-α	Tumour necrosis factor-α
AMPK	AMP-activated protein kinase
TAK1	TGF-β activated kinase-1
FFAR4	Free fatty acid receptor

Introduction

A growing body of research supports the hypothesis that foetal nutrition during the critical developmental period has long-term health effects and that the development of certain disorders in childhood is dependent on nutrition during pregnancy. In 1993, Barker et al. [1] from the University of Southampton, UK were the first to link foetal nutrition to disorders that developed later in life. They demonstrated that individuals with low birth weight had an increased risk of developing coronary heart disease and diabetes; these findings are currently widely accepted. This initial observation led to a new inference that chronic adult diseases are programmed by malnutrition and other deleterious factors in the womb.

Pregnancy in diabetic women is associated with a wide variety of risks. In particular, hyperglycaemia during pregnancy has been shown to be associated with many complications in infants [2]. Among these, an increased risk of cardiomyocyte hypertrophy as a cardiovascular complication in IDMs was previously reported to be a result of poor glycaemic control during the intrauterine foetal development [3] (Fig. 14.1). Although some clinical studies demonstrated a number of cardiovascular disorders in IDMs, further elucidation of the underlying molecular mechanisms is required.

Therefore, we developed an animal model of foetal exposure to hyperglycaemia during pregnancy to characterize the pathology observed in the neonatal heart at a molecular level and to identify dietary factors that could improve these pathological alterations via a molecular nutrition-based study. We demonstrated that abnormal insulin signalling-induced insulin resistance through the inhibition of the Akt/mTOR pathway in the neonatal rat heart. Abnormal signalling was improved in the offspring

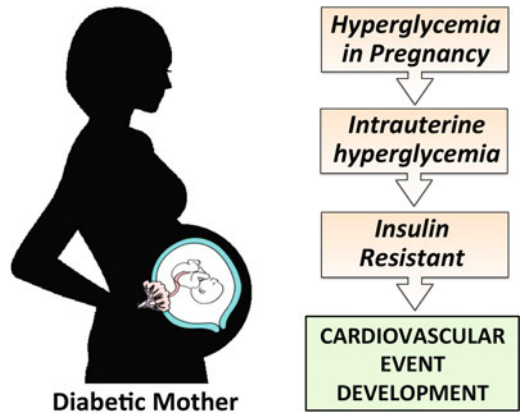


Fig. 14.1 Hyperglycaemia in diabetic mothers induces cardiovascular disease in infants. Intrauterine hyperglycaemia-induced insulin resistance leads to impaired cell signalling in cardiomyocytes of infants

of rats that were fed a fish oil-rich diet during pregnancy [4]. However, the active ingredient(s) of fish oil responsible for the observed improvement in signalling remains unclear. Fish oil is present in a multitude of seafood and is particularly high in fatty fish, which contains high docosahexaenoic acid (DHA) and EPA levels, both of which are omega-3 polyunsaturated fatty acids (PUFAs). The consumption of fish oil was extensively reported to lower plasma triglyceride levels, resting heart rate and blood pressure. Fish oil has been shown to reduce inflammation and improve vascular function. Consequently, the consumption of EPA was associated with improvements in cardiovascular diseases.

This chapter will address several key topics. We will first overview the classification of omega-3 PUFAs and the available data on their many beneficial effects in pregnant women. We will then present our findings demonstrating impaired Akt/mTOR-mediated insulin signalling in neonatal hearts of rats born to diabetic mothers, which can be alleviated by a fish oil-rich maternal diet during pregnancy. Furthermore, we will describe a possible molecular mechanism for omega-3 PUFA-mediated reduction in the risk of cardiovascular diseases using animal models, isolated cardiomyocytes. Lastly, we will discuss the safety of fish oil consumption in pregnant women. EPA may have beneficial effects on foetal heart by providing protection from the hyperglycaemic intrauterine environment in pregnant diabetic women.

Omega-3 PUFAs

Fatty acids are classified into unsaturated and saturated fatty acids. Unsaturated fatty acids contain one or more double bonds in the carbon chain, whereas saturated fatty acids do not contain double bonds (Fig. 14.2). Unsaturated fatty acids are further divided into two subgroups: (1) monounsaturated fatty acids with a single double bond and (2) PUFAs with two or more double bonds. In addition, the position of the double bond in relation to the methyl end determines the PUFA subtypes: omega-3 PUFAs and omega-6 PUFAs [5]. Saturated fatty acids are normally solid and chemically stable at room temperature. They are abundant in animal oil; palmitic acid (PA) and stearic acid are typical representatives of this class. Specifically, PA was reported as a risk factor for cardiovascular diseases [6]. Conversely, intake of saturated fatty acids from milk products was able to provide protection from cardiovascular diseases. However, it is not yet clear if the effect was due to different saturated fatty acid subtypes or another component in milk. In contrast, unsaturated fatty acids are chemically unstable and usually liquid at room temperature. Oleic acid, a monounsaturated fatty acid found in abundance in olive oil, lowers LDL cholesterol in the blood. Linoleic acid and γ-linolenic acid, omega-6 PUFAs found in a variety of vegetable oils such as corn oil and safflower oil, prevent arteriosclerosis and thrombosis via a number of mechanisms such as decreased blood pressure and reduced LDL cholesterol. In addition, arachidonic acid found in egg yolk and liver are synthesized from linoleic acid in the body. Its excessive intake induces allergies, arteriosclerosis and high blood pressure.

EPA, DHA and docosapentaenoic acid are omega-3 PUFAs that are abundant in fish oil and marine algae [7]. Furthermore, α-linolenic acid is abundant in perilla seed oil, flaxseed oil and walnut oil. As higher vertebrates including humans do not have the desaturase enzymes that synthesize α-linolenic acid from linoleic acid, both α-linolenic acid and linoleic acid are essential fatty acids. The efficacy of α-linolenic acid conversion to EPA and DHA is very low, around 10–15%; thus, direct supplementation of EPA and DHA naturally found in fish oil and algae is considered necessary. Furthermore, in premature infants and newborns, the enzymatic activity of desaturases and elongases, both of which are necessary for EPA and DHA biosynthesis, is very low, emphasizing the need for direct ingestion of fish oil rich in EPA and DHA [8].

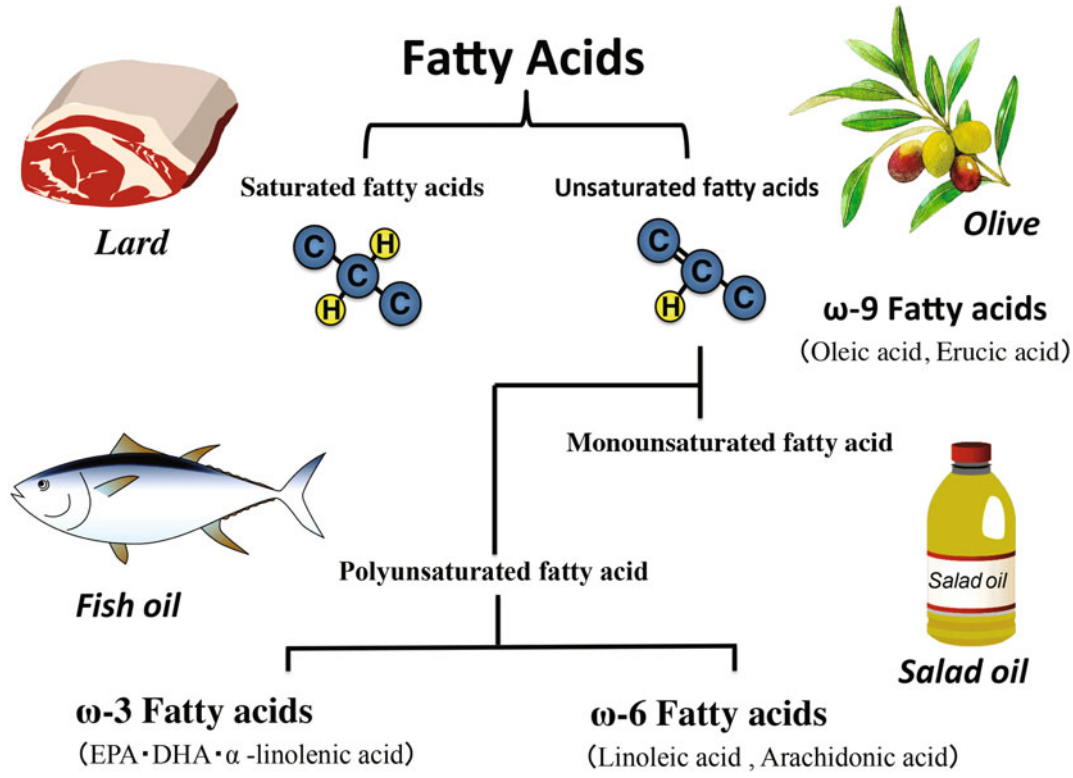


Fig. 14.2 Classification of fatty acids. Fatty acids are classified according to their degree of saturation and number of carbons. In unsaturated fatty acids, the number following the omega symbol (ω) refers to the location of the first double bond (C=C) relative to the methyl end of the molecule. Saturated fatty acids include stearic acid and myristic acid. Among unsaturated fatty acids, oleic acid and erucic acid are omega-9 fatty acids, linoleic acid and arachidonic acid are omega-6 fatty acids and EPA, DHA and α-linoleic acid are omega-3 fatty acids

Omega-3 PUFAs for Pregnant Women

The preventative effect of omega-3 PUFAs abundantly found in fish on cardiovascular diseases became increasingly clear by the Greenland observational studies in 1970s by a Danish group and a Dutch prospective observational study in 1980 [9]. Omega-3 PUFAs were reported to have multi-faceted effects such as improvement of altered lipid metabolism, inhibition of platelet aggregation, vasodilation and stabilization of atherosclerotic plaques [10–12]. Consequently, high-purity EPA and DHA/EPA formulations have been used as adjunctive therapy for hyperlipidaemia and peripheral artery disease in clinical practice [13]. Furthermore, infants were found to benefit from numerous effects of omega-3 PUFAs given to mothers during pregnancy. Several representative examples are detailed below.

Improvement of Asthma and Allergic Disease

Fish oil consumption in late pregnancy was shown to reduce asthma in the offspring [14, 15]. In contrast, while no significant difference in the prevalence of IgE-related allergic diseases was

observed in randomized controlled trials that assessed 1- and 3-year-old children born to mothers who consumed DHA-rich fish oil during pregnancy, there was a significant difference in egg allergy prevalence [16, 17].

Improvement of Cognitive Function

Initiation of fish oil consumption at 20 weeks of gestation showed significant improvement in hand and eye coordination in the offspring of mothers that received fish oil supplementation when children were evaluated at 2½ years of age. While there was a significant correlation between the observed improvements and concentration of omega-3 PUFAs in umbilical cord blood, omega-6 PUFAs showed an inverse correlation with the parameters assessed [18]. Furthermore, fish oil supplementation during pregnancy did not affect cognition, language or fine motor skills of patients when they were evaluated again at approximately 12 years of age. However, a significant correlation between the DHA concentration in red blood cells and IQ testing was observed in these children [19].

Prevention of Miscarriage

Miscarriage occurs in 15–20% of all pregnancies. In addition, some women who experience repeated miscarriages have an autoimmune condition called antiphospholipid syndrome. Fish oil was demonstrated to prevent recurrent miscarriage in women with antiphospholipid antibody syndrome and a history of miscarriage [20, 21].

Prevention of Preterm Birth

Preterm births are linked to adverse outcomes in infants. There is limited evidence suggesting that consumption of fish oil or fish-derived omega-3 PUFAs during pregnancy might reduce the likelihood of preterm birth and increase birth weight [22]. For example, ingestion of 600 mg DHA per day in the latter half of gestation led to reductions in the rates of early preterm birth and very low birth weight [23]. Japan and Iceland have the lowest rates of neonatal (<28 days) mortality per 1000 live births based on data from the United Nations Inter-Agency Group for Child Mortality Estimation [24]. These relatively low mortality rates might be due to the relatively high consumption of fish oil in these two countries.

Improvement of Impaired Akt/mTOR-Mediated Insulin Signalling by Fish Oil

We developed a rat model of diabetic pregnancy in which impaired insulin secretion developed following targeted destruction of the pancreatic β cells via intravenous streptozotocin (600 mg kg^{-1} body weight) administration through the tail vein. In this diabetic pregnant rat model, the rate of stillbirth was higher than the control group when the animals were fed a high-fat lard diet (fat content: 56.7%) during pregnancy [25], suggesting that a high-fat diet in addition to a hyperglycaemic intrauterine environment might exacerbate cardiovascular events. Thus, we examined signalling

pathways in the neonatal hearts in this animal model to test two hypotheses: (1) supplementation with fish oil containing high levels of omega-3 PUFAs in pregnant diabetic mothers exerts beneficial effects on cardiac development in their offspring through the placenta and (2) lard, which contains high levels of unsaturated fatty acids, is detrimental to cardiac development in the offspring of diabetic mothers. The pregnant diabetic rats were given either a fish oil diet containing unsaturated fatty acids, a lard diet containing saturated fatty acids or a normal feed starting from day one of pregnancy. Afterwards, the infants were analysed [4]. We examined the Akt/mTOR-mediated insulin signalling pathway, which was proposed to play a key role in cardiac glucose uptake, using Western blotting.

During insulin signalling, receptor activation leads to the phosphorylation of key tyrosine residues on insulin receptor substrate (IRS) proteins, with subsequent recruitment of Akt to the plasma membrane. Akt activation also requires phosphorylation by phosphoinositide-dependent protein kinase-1 and mTOR, and Akt activation can induce glucose transporter type 4 (GLUT4) translocation. Alteration of this signalling pathway results in insulin resistance. Therefore, the inhibition of Akt phosphorylation is an important indicator of insulin resistance. Insulin resistance can also be induced by inhibition of Akt activation as well as by reactive oxygen species and endoplasmic reticulum stress triggered by hyperglycaemia via activation of mitogen-activated protein kinase (MAPK) [26] (Fig. 14.3). Our results revealed abnormal Akt-related insulin signalling in neonatal hearts of rats

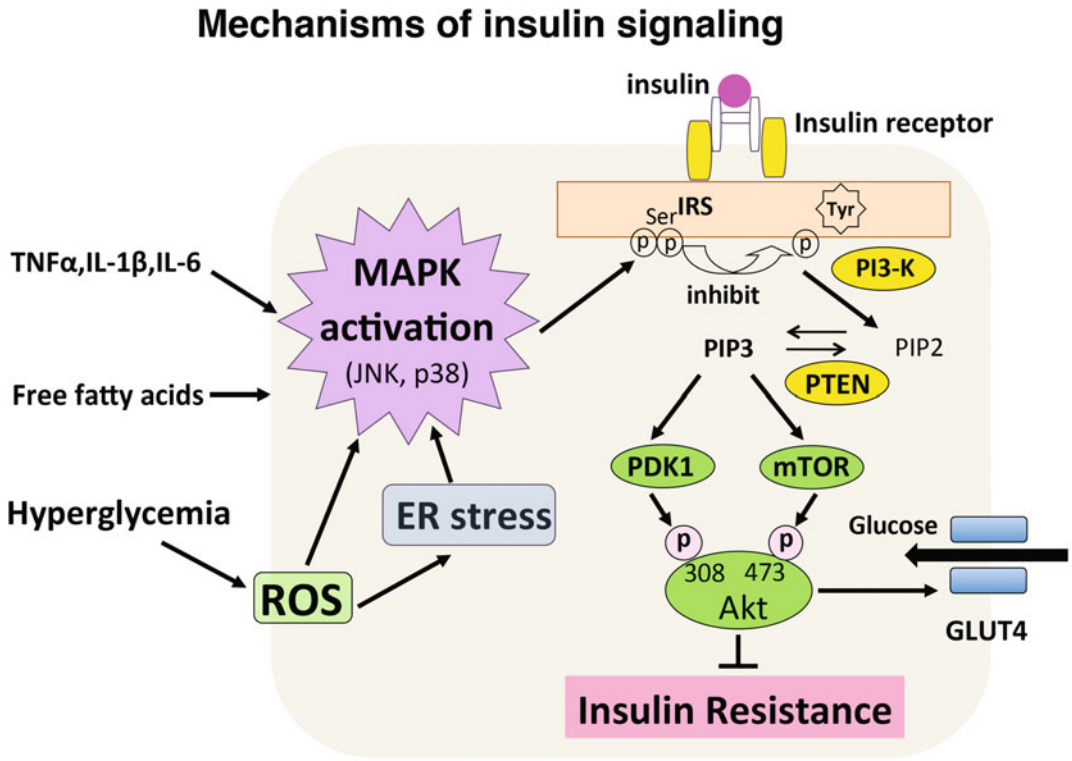


Fig. 14.3 Mechanisms of insulin signalling. In insulin signalling, receptor activation leads to the phosphorylation of key tyrosine residues on IRS proteins. Through autophosphorylation of IRS, Akt is recruited to the plasma membrane. Activation of Akt also requires phosphorylation by PDK1 and mTOR. Activation of Akt induces GLUT4 translocation. Inhibition of Akt activation indicates insulin resistance. ROS and ER stress induced by hyperglycaemia also cause insulin resistance via activation of MAP kinase. Abbreviations *IR* insulin receptor; *IRS* insulin receptor substrate; *PI3K* phosphoinositide 3-kinase; *PTEN* phosphatase and tensin homolog deleted from chromosome 10; *PDK1* 3-phosphoinositide-dependent protein kinase 1; *ROS* reactive oxygen species; *ER* endoplasmic reticulum; *GLUT4* glucose transporter type 4

born to diabetic mothers [4]. Furthermore, compared with the control rats, the cardiac tissue of experimental animals exhibited lower levels of mTOR expression and reduced Akt phosphorylation at amino acids Thr-308 and Ser-473, with concomitant reductions in phosphorylation of p38 and c-Jun N-terminal kinase (JNK) (Fig. 14.4). Conversely, the cardiac tissue of offspring born to mothers that were fed the fish oil diet exhibited improved levels of phospho-Akt 473, phospho-p38, JNK and mTOR compared with those detected in the offspring of mothers that were fed the lard-based diet (Fig. 14.4). Hyperglycaemia, which was observed in the offspring of diabetic mothers at postnatal day 1, might be partially due to a residual effect of perinatal sharing of blood between the mother and foetus. Incidentally, there was no significant difference in blood glucose levels between the offspring of diabetic mothers and those of control mothers on postnatal day 4 (Table 14.1), suggesting that blood glucose levels were normalized by postnatal day 4 in infants born to diabetic mothers. Interestingly, the Akt/mTOR-mediated insulin signalling remained dysregulated despite normalization of blood glucose levels at postnatal day 4; this dysregulation was augmented further by the lard-based diet. However, the Akt-mTOR-mediated insulin signalling was improved in infants born to mothers that received the fish oil diet [4]. Moreover, both the blood glucose and triglyceride levels at postnatal day 1 were lower in the offspring of mothers that were fed the fish oil diet than in those born to mothers that were fed the high lard-based diet [4]. These results together suggested that fish oil

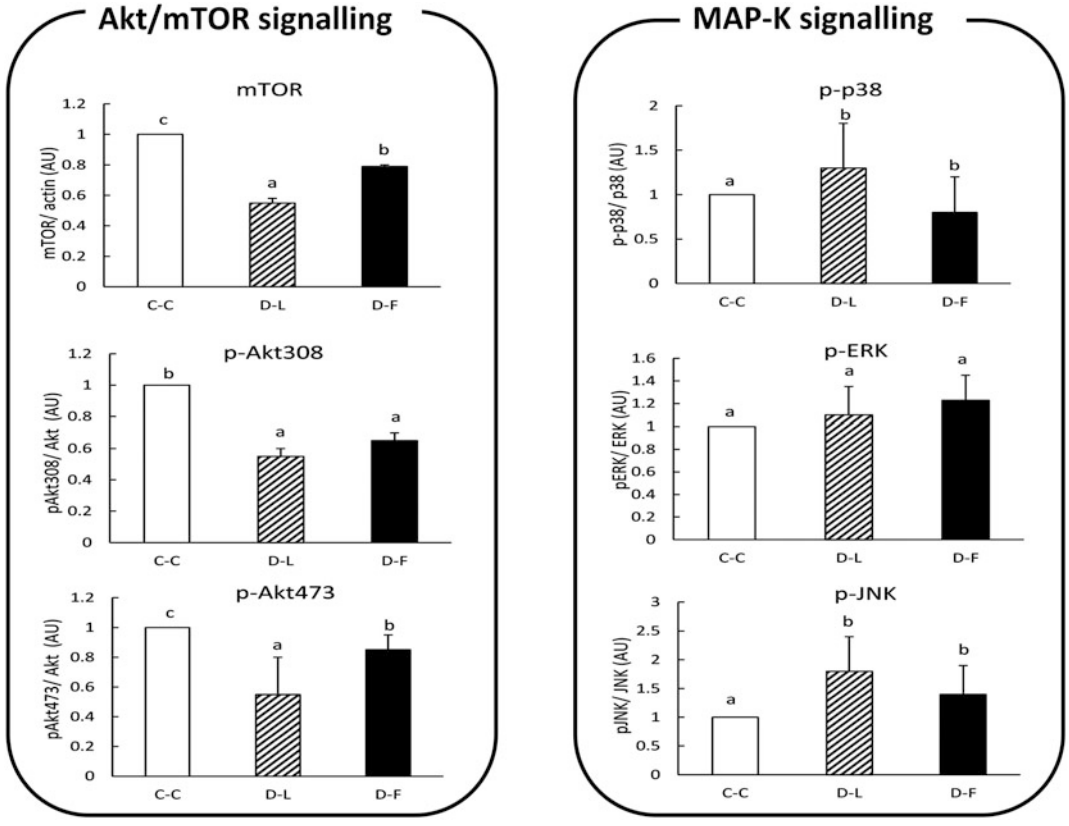


Fig. 14.4 Effect of hyperglycaemia on Akt/mTOR and MAP-K. Effect of hyperglycaemia on the phosphorylation levels of Akt (p-Akt 308 and p-Akt 473) and components of the MAP-K pathway (p-p38, p-ERK and p-JNK) and expression level of mTOR in neonatal rat heart by Western blot analysis. C-C: Infants born to mothers that were fed a control diet. D-L: infants born to diabetic mothers that were fed a lard diet. D-F: infants born to diabetic mothers that were fed a fish oil diet. Values are expressed as mean ± SEM (n = 10 per group). Mean in a column without a common letters. $P < 0.05$

Table 14.1 Blood glucose and triglyceride levels in the offspring of diabetic rats

		C-C	D-L	D-F
Blood glucose level (mg/dL)	Postnatal day 1	a 115.3 ± 13.4	c 390.3 ± 20.0	b 328.3 ± 24.7
	Postnatal day 4	120.8 ± 20.1	131.2 ± 13.4	128.8 ± 11.8
Triglyceride level (mg/dL)		b 121.5 ± 16.2	b 150.5 ± 33.1	a 86.7 ± 11.5

[1]Values represent means ± SEM. $n = 10$ per group. Means in a column without a common letter differ, $P < 0.05$

might improve impaired Akt/mTOR-mediated insulin signal. As fish oil is known to improve lipid metabolism and stillbirth rates in children, several critical questions arose based on our initial findings in this model. First, why dose led to impaired Akt/mTOR-mediated insulin signalling in the heart of infants born to diabetic rats? Second, the mechanism underlying the effect of fish oil ingestion on dysregulated insulin signalling in the heart was not clear. In addition, identification of the specific component that led to improvement in this model was required. Therefore, we first explored several known components of fish oil for their ability to alleviate impaired Akt/mTOR-mediated insulin signalling. While fish oil is rich in EPA and DHA, we focused on EPA for two reasons. First, DHA is efficiently converted from EPA by elongase in humans. Second, EPA was protective against cardiovascular events. Thus, EPA was administered to pregnant diabetic rats via a gastric tube, and its effects on insulin signalling were evaluated in the neonatal heart. In addition, we examined the effect of EPA on cultures of primary rat cardiomyocytes isolated from the cardiac tissue of neonates born to diabetic mothers. Similar to our previously reported findings, in both in vivo and in vitro models, the impaired Akt/mTOR-mediated insulin signalling was improved in both the heart tissue and cultured primary cardiomyocytes of infants born to diabetic mothers that were administered oral EPA (unpublished observations). Thus, it is highly likely that EPA is one of the active components initiating the beneficial effects of fish oil that were observed in our previous study. Moreover, cardiomyocytes that were isolated from neonatal rats born to diabetic mothers exhibited impaired insulin signalling, reduced activation of the Akt/mTOR-mediated insulin cascade and reduced GLUT4 translocation (unpublished observations).

Molecular Mechanisms of Fish Oil-Mediated Improvement of Cardiovascular Events

The United Kingdom Prospective Diabetes Study [27] was an important investigation that examined the effect of glycaemic control on cardiovascular events. The findings of the study clearly demonstrated that strict glycaemic control could suppress the onset and progression of microvascular complications and provided strong evidence for the close relationship between diabetes and cardiovascular events. Therefore, EPA as a fish oil constituent is used in clinical practice for its cardiovascular protective effects. The molecular mechanisms underlying this effect of fish oil, which have been recently defined in several in vitro and in vivo studies, include (1) endothelin-1 (ET-1)-induced cardiac hypertrophy, (2) PA-induced cardiomyocyte dysfunction and (3) G protein-coupled receptor (GPCR) activation by omega-3 PUFAs.

ET-1 and Endothelial Dysfunction

The expression of ET-1 was shown to increase in endothelial cells with the progression of diabetes. Thus, ET-1 and nitric oxide secretion by endothelial cells were hypothesized to be significantly involved in diabetic complications [28]. In experiments using human umbilical vein endothelial cells (HUVECs), ET-1 secretion was increased with exposure of HUVECs to insulin [29]. In addition, ET-1 secretion from vascular endothelial cells of newborn rats led to the induction of MAPK signalling and stress-induced cardiomyocyte hypertrophy [30]. However, EPA was also shown to reduce insulin-mediated ET-1 gene expression in HUVECs [31]. Furthermore, in an ET-1-induced cardiac hypertrophy model, EPA prevented cardiac hypertrophy via suppression of NADPH oxidase, transforming growth factor β1 (TGF-β1) and phosphorylated JNK as well as through upregulation of the peroxisome proliferator-activated receptor-α signalling pathway [32, 33]. In addition, in a rat model of type 2 diabetes (Otsuka Long-Evans Tokushima Fatty rats), EPA ameliorated endothelial dysfunction by correcting the imbalance between endothelium-derived factors through reducing the activities of extracellular-signal-regulated kinases and nuclear factor κB (NF-κB) [34]. Thus, EPA from fish oil was demonstrated to improve myocardial hypertrophy by inhibiting MAPK signalling induced by ET-1 secreted from endothelial cells (Fig. 14.5).

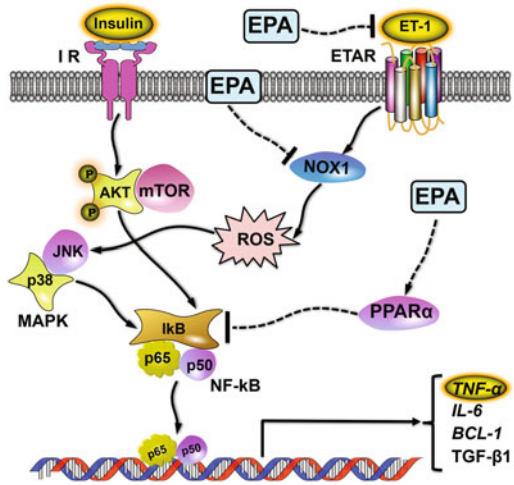


Fig. 14.5 Induction of ET-1 gene expression by hyperglycaemia. Hyperglycaemia activates MAPK and Akt/mTOR and induces expression of inflammatory cytokines, oxidative stress and apoptosis via activation of the nuclear factor (NF)-κB pathway (IκB, p50 and p60). Hyperglycaemia also induces ET-1 gene expression. ET-1 increases the expression of NOX and TGF-β1 and phosphorylation of JNK. NOX induces ROS. EPA prevents cardiomyocyte hypertrophy via suppression of NOX, TGF-β1 and JNK as well as upregulation of PPARα. Abbreviations *IR* insulin receptor; *EPA* eicosapentaenoic acid; *ET-1* endothelin-1; *ETAR* endothelin A receptor; *NOX1* NADPH oxidase 1; *ROS* reactive oxygen species; *ER* endoplasmic reticulum; *TFN-α*, tumour necrosis factor-α; *TGF-β1* transforming growth factor β1; *IL-6* interleukin-6; *NF-κB* nuclear factor κB; *MAPK* mitogen-activated protein kinase; *JNK* c-Jun N-terminal kinase; *mTOR* mammalian target of rapamycin; *PPARα* peroxisome proliferator-activated receptor-α

Cardiomyocyte Dysfunction Induced by PA

PA, a saturated fatty acid, is widely recognized for its ability to cause cardiomyocyte dysfunction [35]. Expression of inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 in cardiomyocytes were shown to be induced by PA [36–38]. Furthermore, apoptosis of cardiomyocytes and insulin resistance induced by these inflammatory cytokines were demonstrated to result from NF-κB activation downstream from MAPK signalling and through impaired Akt/mTOR-mediated insulin signalling [39–41]. Interestingly, EPA could counteract PA-induced insulin resistance and apoptosis via increasing the levels of phosphorylated Akt and phosphorylated AMP-activated protein kinase (AMPK) [42–45]. These findings provide further support for the beneficial effect of EPA, which led to the improvement in impaired Akt/mTOR-mediated insulin signalling that was observed in the heart of neonate rats born to diabetic mothers fed a fish oil-rich diet during pregnancy (Fig. 14.6).

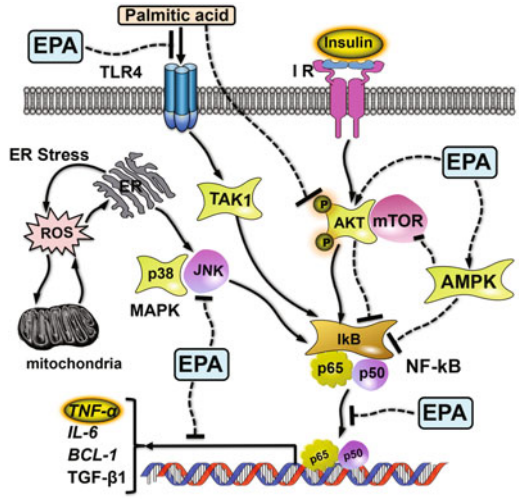


Fig. 14.6 Induction of insulin resistance by PA. PA-induced insulin resistance is mediated by the proinflammatory receptor TLR4. EPA inhibits TLR4 signalling by blocking the binding of PA to TLR4. Abbreviations *IR* insulin receptor; *EPA* eicosapentaenoic acid; *ROS* reactive oxygen species; *ER* endoplasmic reticulum; *TFN-α* tumour necrosis factor-α; *TGF-β1* transforming growth factor β1; *IL-6* interleukin-6; *NF-κB* nuclear factor κB; *TLR4* toll-like receptor 4; *MAPK* mitogen-activated protein kinase; *JNK* c-Jun N-terminal kinase; mTOR, mammalian target of rapamycin; *TAK1* TGF-β activated kinase-1

GPCR Activation by EPA

Cell membrane receptors that specifically bind to EPA have not yet been identified. However, both EPA and DHA were recently demonstrated as ligands specific for GPR120, an orphan GCPR [46]. In patients with heart failure, cytokine production from inflammatory macrophages in adipose tissue was reduced by binding of omega-3 PUFAs to GPR120, resulting in alleviated insulin resistance [47]. This interaction inhibits TGF-β activated kinase-1 (TAK1) through β-arrestin 2/TAK1 binding protein-1, which provides potent anti-inflammatory effects by inhibiting the Toll-like receptor and TNF-α signalling pathways [48, 49]. Recently, GPR120 was designated as a free fatty acid receptor (FFAR4), and agonists of FFAR4 have attracted attention as potential drug targets for geriatric diseases such as diabetes and obesity [50] (Fig. 14.7). Based on the accumulating evidence, the role of GPR120 in the protective effect of EPA in cardiomyocytes should be further investigated.

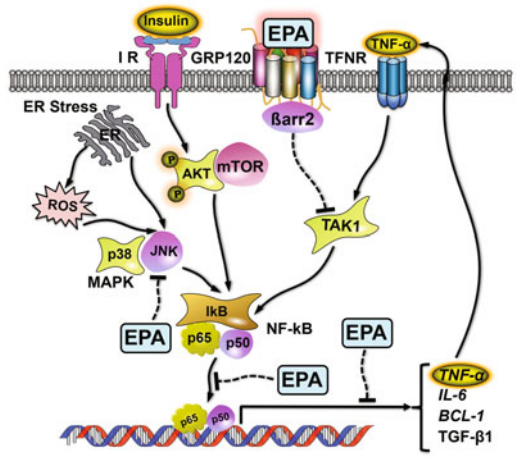


Fig. 14.7 EPA binding to GPR120 induces insulin resistance. TFN-α expression is increased following expression of the NF-κB target gene via TAK1 activation. EPA is a specific ligand for GPR120. Activation of GPR120 following EPA binding leads to its internalization and complex formation with βarr2 to form the GPR120/βarr2 complex. This complex inhibits TAK1 and prevents downstream NF-κB and JNK signalling pathway. Abbreviations *IR* insulin receptor; *EPA* eicosapentaenoic acid; *ROS* reactive oxygen species; *ER* endoplasmic reticulum; *TFN-α* tumour necrosis factor-α; *TFNR* tumour necrosis factor-α receptor; *TGF-β1* transforming growth factor β1; *IL-6* interleukin-6; *NF-κB* nuclear factor κB; *MAPK* mitogen-activated protein kinase; *JNK* c-Jun N-terminal kinase; *mTOR* mammalian target of rapamycin; *TAK1* TGF-β activated kinase-1; *GPR120* G protein-coupled receptor 120; *βarr2* β-arrestin-2

Conclusions

Our recently characterized model of intrauterine hyperglycaemia during pregnancy has revealed several adverse events occurring at the molecular level during foetal heart development. We showed that abnormal insulin signalling induced insulin resistance through inhibition of the Akt/mTOR pathway in the heart of neonatal rats. Importantly, the impaired signalling was improved in the offspring of rats that were fed a fish oil-rich diet. In addition, we determined that one ingredient of fish oil that exerted this effect was EPA. We further described several recent findings showing molecular mechanisms underlying the inhibitory effect of omega-3 PUFAs on cardiovascular events. To avoid a negative impact on normal foetal development, nutritional therapy using dietary management and supplements should be preferred over drug therapies. One major concern related to fish oil supplementation is the worsening of marine pollution. Fish oil rich in omega-3 PUFAs contains heavy metals such as mercury, cadmium and lead as well as toxic compounds such as dioxin and polychlorinated biphenyl. Thus, sufficient attention should be paid to the source as well as the amount of fish oil ingestion. α-linolenic acid in flaxseed oil and perilla seed oil are considered as alternatives to replace fish oil supplements. However, given the poor efficacy of α-linolenic acid conversion to EPA and DHA in humans, the high-quality omega-3 PUFAs contained in fish oil remains as the more attractive source. Based on the deleterious effects of toxic compounds due to marine pollution and bioaccumulation, the use and source of EPA formulations for consumption are likely going to be the focus of discussion in the future. Compared with other countries, Japan enjoys a very low incidence of preterm birth and a very long average life span. For Japanese people living in an island nation, which is surrounded by sea, obtaining a blessing from the sea since ancient times might have led to these outcomes.

Acknowledgements This study was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15K00809 to AN and 26750054 to RK) and a grant from the Smoking Research Foundation (to AN).

References

1. Barker DJ, Gluckman PD, Godfrey KM, et al. Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;10: 341(8850):938–41.
2. Driscoll SG, Benirschke K, Curtis GW. Neonatal deaths among infants of diabetic mothers. Postmortem findings in ninety-five infants. Am J Dis Child. 1960;100:818–35.
3. Hay WW Jr. Care of the infant of the diabetic mother. Curr Diab Rep. 2012;12(1):4–15.
4. Nasu-Kawaharada R, Nakamura A, Kakarla SK, et al. A maternal diet rich in fish oil may improve cardiac Akt-related signaling in the offspring of diabetic mother rats. Nutrition. 2013;29(4):688–92.
5. Food and Nutrition Board, Institute of Medicine. Dietary Fats: Total Fat and Fatty Acids. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press; 2002:422–541.
6. de Oliveira Otto MC, Mozaffarian D, Kromhout D, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Am J Clin Nutr. 2012;96(2):397–404.
7. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr. 2000;71(1 Suppl):179S–88S.
8. Foreman-van Drongelen MMHP, Westdorp JM, van Houwelingen AC, et al. The essential fatty acid status of premature infants and the fatty acid composition of their diet. Am J Clin Nutr. 1993;57:829S.
9. Dyerberg J, Bang HO, Stoffersen E, et al. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet. 1978; 2(8081): 117–110.
10. Myhrstad MC, Retterstøl K, Telle-Hansen VH, et al. Effect of marine n-3 fatty acids on circulating inflammatory markers in healthy subjects and subjects with cardiovascular risk factors. Inflamm Res. 2011;60:309–19.
11. Phang M, Garg ML, Sinclair AJ. Inhibition of platelet aggregation by omega-3 polyunsaturated fatty acids is gender specific-redefining platelet response to fish oils. Prostagland Leukotr Ess. 2009;81:35–40.

12. Marchioli R, Barzi F, Bomba E, et al. GISSI-Prevenzione Investigators.: early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time course analysis of the Gruppo Italiano per lo Stuio deela Sopravivenza nell' Infarcto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105:1897–903.
13. Yokoyama M, Origasa H, Matsuzaki M, et al. Japan EPA lipid intervention study (JELIS) Investigators: effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007; 31; 369 (9567): 1090–8.
14. Olsen SF, Østerdal ML, Salvig JD, et al. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring. 16 y of registry-based follow-up from a randomized controlled trial. Am J Clin Nutr. 2008;88:167–75.
15. Yang H, Xun P, He K. Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. PLoS ONE. 2013;8:e80048.
16. Palmer DJ, Sullivan T, Gold MS, et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. BMJ. 2012;30(344):e184.
17. Palmer DJ, Sullivan T, Gold MS, et al. Randomized controlled trial of fish oil supplementation in pregnancy on childhood allergies. Allergy. 2013;68(11):1370–6.
18. Dunstan JA, Simmer K, Dixon G, et al. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008;93:F45–50.
19. Meldrum S, Dunstan JA, Foster JK, et al. Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial. Nutrients. 2015;7:2061–7.
20. Rossi E, Costa M. Fish oil derivatives as a prophylaxis of recurrent miscarriage associated with antiphospholipid antibodies (APL): a pilot study. Lupus. 1993;2:319–23.
21. Lazzarin N, Vaquero E, Exacoustos C, et al. Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertil Steril. 2009;92:296–300.
22. Salvig JD, Lamont RF. Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2011;90:825–38.
23. Carlson SE, Colombo J, Gajewski BJ, et al. DHA supplementation and pregnancy outcomes. Am J Clin Nutr. 2013;97(4):808–15.
24. The United Nations Inter-Agency Group for Child Mortality Estimation. http://www.childmortality.org. Accessed 9 Sept 2015.
25. Nasu R, Seki K, Nara M, et al. Effect of a high-fat diet on diabetic mother rats and their offspring through three generations. Endocr J. 2007;54(4):563–9.
26. Bertrand L, Horman S, Beauloye C, et al. Insulin signalling in the heart. Cardiovasc Res. 2008;79:238–48.
27. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352: 837–53.
28. Bauer V, Sotníková R. Nitric oxide the endothelium-derived relaxing factor and its role in endothelial functions. Gen Physiol Biophys. 2010;29:319–40.
29. Mitchell MD, Branch DW, Lamarche S, et al. The regulation of endothelin production in human umbilical vein endothelial cells: unique inhibitory action of calcium ionophores. J Clin Endocrinol Metab. 1992;75:665–8.
30. Yamazaki T, Komuro I, Kudoh S, et al. Endothelin-1 is involved in mechanical stress-induced cardiomyocyte hypertrophy. J Biol Chem. 1996;271:3221–8.
31. Chisaki K, Okuda Y, Suzuki S, et al. Eicosapentaenoic acid suppresses basal and insulin-stimulated endothelin-1 production in human endothelial cells. Hypertens Res. 2003;26:655–61.
32. Shimojo N, Jesmin S, Zaedi S. Eicosapentaenoic acid prevents endothelin-1-induced cardiomyocyte hypertrophy in vitro through the suppression of TGF-beta 1 and phosphorylated JNK. Am J Physiol Heart Circ Physiol. 2006;291:H835–45.
33. Shimojo N, Jesmin S, Sakai S, et al. Fish oil constituent eicosapentaenoic acid inhibits endothelin-induced cardiomyocyte hypertrophy via PPAR-α. Life Sci. 2014;118:173–8.
34. Matsumoto T, Nakayama N, Ishida K, et al. Eicosapentaenoic acid improves imbalance between vasodilator and vasoconstrictor actions of endothelium-derived factors in mesenteric arteries from rats at chronic stage of type 2 diabetes. J Pharmacol Exp Ther. 2009;329:324–34.
35. Drosatos K, Schulze PC. Savings precede spending: fatty acid utilization relies on triglyceride formation for cardiac energetics. Circulation. 2014;130:1775–7.
36. Jové M, Planavila A, Sánchez RM, et al. Palmitate induces tumor necrosis factor-alpha expression in C2C12 skeletal muscle cells by a mechanism involving protein kinase C and nuclear factor-kappa B activation. Endocrinology. 2006;147:552–61.
37. Zhang J, Wu W, Li D, et al. Overactivation of NF-κB impairs insulin sensitivity and mediates palmitate-induced insulin resistance in C2C12 skeletal muscle cells. Endocrine. 2010;37:157–66.

38. Alvarez-Guardia D, Palomer X, Coll T, et al. PPARβ/δ activation blocks lipid-induced inflammatory pathways in mouse heart and human cardiac cells. Biochim Biophys Acta. 2011;1811:59–67.
39. Wei CD, Li Y, Zheng HY, et al. Globular adiponectin protects H9c2 cells from palmitate-induced apoptosis via Akt and ERK1/2 signaling pathways. Lipids Health Dis. 2012;11:135.
40. Park M, Sabetski A, Kwan CY, et al. Palmitate induces ER stress and autophagy in H9c2 cells: implications for apoptosis and adiponectin resistance. J Cell Physiol. 2015;230:630–9.
41. Hsu HC, Chen CY, Lee BC, et al. High-fat diet induces cardiomyocyte apoptosis via the inhibition of autophagy. Eur J Nutr. 2016; 55:2245–54.
42. De Mello VD, Erkkilä AT, Schwab US, et al. The effect of fatty or lean fish intake on inflammatory gene expression in peripheral blood mononuclear cells of patients with coronary heart disease. Eur J Nutr. 2009;48: 447–55.
43. Cetrullo S, Tantini B, Flamigni F, et al. Antiapoptotic and antiautophagic effects of eicosapentaenoic acid in cardiac myoblasts exposed to palmitic acid. Nutrients. 2012;4:78–90.
44. Hsu HC, Chen CY, Chiang CH, et al. Eicosapentaenoic acid attenuated oxidative stress-induced cardiomyoblast apoptosis by activating adaptive autophagy. Eur J Nutr. 2014;53:541–7.
45. Franekova V, Angin Y, Hoebers NT, et al. Marine omega-3 fatty acids prevent myocardial insulin resistance and metabolic remodeling as induced experimentally by high insulin exposure. Am J Physiol Cell Physiol. 2015;308: C297–307.
46. Talukdar S, Olefsky JM, Osborn O. Targeting GPR120 and other fatty acid-sensing GPCRs ameliorates insulin resistance and inflammatory diseases. Trends Pharmacol Sci. 2011;32: 543–50.
47. Kazemian P, Kazemi-Bajestani SM, Alherbish A, et al. The use of ω-3 poly-unsaturated fatty acids in heart failure: a preferential role in patients with diabetes. Cardiovasc Drugs Ther. 2012;26:311–20.
48. Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell. 2010;142:687–98.
49. Ichimura A, Hirasawa A, Poulain-Godefroy O, et al. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. Nature. 2012;483:350–4.
50. Oh DY, Walenta E, Akiyama TE, et al. Gpr120-selective agonist improves insulin resistance and chronic inflammation in obese mice. Nat Med. 2014;8:942–7.

Part V
Pre-existing Conditions and Gestational Diabetes Risk

Chapter 15
Hypertensive Disorders of Pregnancy in Gestational Diabetes

Beatriz Barquiel and Paola Parra

Key Points

- Hypertensive disorders of pregnancy may be an expression of insulin resistance in women with gestational diabetes. Insulin resistance may be present prior to pregnancy or developed within gestation, and may persist after delivery.
- Meta-inflammation, oxidative stress and immune reactivity are pathways to hypertensive disorders of pregnancy that may be modulated by action of insulin and converge in the occurrence of endothelial dysfunction.
- Maternal age, ethnic predisposition, obesity, diabetes, chronic hypertension, smoking habit, glycemic control and weight gain are factors that amplify the normal increment of insulin resistance in pregnancy.
- In women with gestational diabetes mellitus, there is an independent and relevant effect of glycemic control and of weight gain on the risk of hypertensive disorders of pregnancy.
- Both hypertensive disorders of pregnancy and gestational diabetes mellitus entail a risk for cardiovascular disease early in life.

Keywords Gestational diabetes · Obesity · Gestational weight gain · Pregnancy-induced hypertension · Preeclampsia · Pregnancy outcome

Abbreviations

HDP	Hypertensive disorders of pregnancy
GDM	Gestational diabetes mellitus
TNF	Tumoral necrosis factor
BP	Blood pressure
CI	Confidence interval
OGTT	Oral glucose tolerance test
IGT	Impaired glucose tolerance
IFG	Impaired fasting glucose

B. Barquiel (✉) · P. Parra
Diabetes Unit and Endocrinology Department, La Paz University Hospital,
Paseo de la Castellana 261, 28046 Madrid, Spain
e-mail: beatriz.barquiel@gmail.com

P. Parra
e-mail: paprch@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_15

Introduction

Hypertensive disorders of pregnancy (HDP) are connected to gestational diabetes mellitus (GDM) [1]. HDP affects 5–7% of pregnancies and 10–28% of those with GDM [2]. This association is mediated by glycemic control, obesity, and gestational weight gain as clinical risk factors that are modifiable [3–7]. GDM is related to HDP, late (>34 weeks) and postpartum HDP [8]. Likely, hyperglycemia and circulation of lipid products contribute to meta-inflammation, oxidative stress, and impairment of immunity that alter the endothelium function at the placenta [9]. Insulin resistance may be at the background of these phenomena. A more strong association with late HDP is plausible in women that develop insulin resistance and GDM toward mid-pregnancy. Insulin resistance prior to pregnancy may facilitate abnormal and insufficient placentation in women with obesity, impaired glucose tolerance, chronic hypertension, or smoking habit [10, 11]. Restriction of fetal growth may be more pronounced in them. Small for gestational age birthweight, indicated preterm delivery and maternal organ dysfunction may be additional consequences of HDP [8]. Chronic hypertension, dyslipidemia and visceral obesity are frequently observed after delivery [12]. These components of metabolic syndrome entail an increased risk of cardiovascular disease in middle-aged women with history of HDP [13, 14]. Pregnancy offers a window of opportunity to detect, follow and treat cardiovascular disease at its earlier stage in these high-risk women.

Origins and Risk of Hypertensive Disorders of Pregnancy

The concept of HDP includes gestational hypertension and preeclampsia. These unexplained disorders are developed during the second half of pregnancy, disappear after delivery or at the puerperium and are manifested with arterial hypertension and/or limbs edema with or without proteinuria or organ dysfunction [15].

Pathogenic theories are redundant on an abnormal placentation plus an immune dysfunction that lead to activation and damage of the endothelium. There is an absence of the second trophoblast invasion of the spiral arteries of the placenta at the union of the decidua and the myometrium from the 16th week of gestation. Cytotrophoblasts do not properly line and substitute the endothelial and muscle cells of the vascular walls. Spiral arteries do not transform into the dilated nonresistant vessels that allow a smooth uteroplacental flow. The persistence of the muscular structure configures the hypertrophic vasculopathy that characterizes the pathology. This hypertrophy leads to hypoperfusion and therefore renin synthesis. The endothelium dysfunction of the placenta is sustained by this activated renin–angiotensin–aldosterone system added to impaired acetylcholine-mediated vasodilation and predominance of thromboxane over prostanoids activity. The renin cascade contributes to an imbalance between the vasoconstrictors angiotensin II and aldosterone and the vasodilator prostaglandins I2 and E1. The vasoconstrictor effect of thromboxane A2 adds an effect as hypercoagulability of pregnancy progresses [9, 16].

One origin of the imbalance toward vasoconstriction and hypercoagulability seems to be in dysfunctions of the immune system. Systemic autoantibodies, fetal–maternal alloimmunity and activation of general systemic immunity may be in the link between immunity and preeclampsia. Related autoimmune phenomena include the presence of antiphospholipid, antilaminin, and antiendothelial antibodies. Other source of autoimmunity is against the antigens of HLA DR typing of the fetus. This reactivity induces immune complexes of fetal–maternal autoantibodies that precipitate and activate the complement system. The general immune response is added. This includes a deficiency of lymphocytes T helper (CD4+) and an activation of neutrophils that liberate leukotriene A4. This molecule is converted to leukotriene C4 by the endothelial cells. Leukotriene C4 is a potent

vasoconstrictor and platelets activator. In addition, neutrophils liberate oxygen free radicals such as nitric oxide. These products of immunity dysfunction generate a destruction of endothelial cells and an increase in permeability and reactivity of the smooth muscle in capillary vessels of the placenta. The endothelial reactivity induces the liberation of other substances, for example endothelin, that feed a loop of vascular constriction and thrombosis. The endothelial damage may be extended to target organs such as kidney or the brain in a complicated preeclampsia [16].

Maternal components of metabolic syndrome may contribute to this imbalance (Fig. 15.1). Visceral adiposity, insulin resistance and hyperinsulinemia, associated arterial hypertension and dyslipidemia are elements of metabolic syndrome. Hyperinsulinemia further activates renin and therefore natriuresis is reduced. In addition, hyperinsulinemia associates an increase in plasma levels of epinephrine and VLDL particles. The liver and the endothelial cell secrete VLDL and VLDL remnants in response to an impaired lipogenic action of insulin. At a molecular level, insulin resistance stimulates the production of type 1 plasminogen activator inhibitor and tumoral necrosis factor (TNF)-α. These factors are involved in placental vessels constriction and endothelial dysfunction. Maternal central obesity contributes to an increased production of TNF-α in adipose tissue. The hyper activated and insulin resistant adipocyte may be a crucial link between metabolic syndrome, GDM, and HDP [17, 18].

The interaction between insulin resistance pathways and abnormal placentation of HDP remains unknown. Noticeably, aberrant gene expression normalizes in cultures of cytotrophoblasts extracted from placentas affected by preeclampsia. For example, the normalized expression of SEMA3B contributes to restore the pathway of vascular endothelial growth factor through the kinase activities of PI3/AKT and GSK3 [19]. The reversibility of these changes suggests a role of the microenvironment at the uterus in modulation of genetic and epigenetic changes that lead to HDP. In this sense,

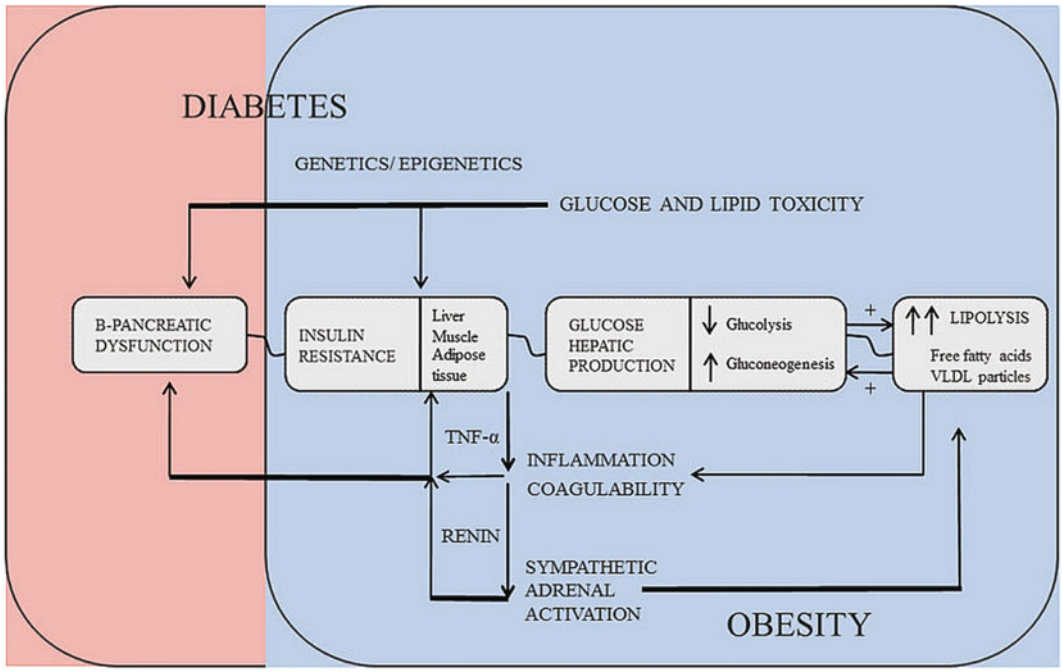


Fig. 15.1 Metabolic pathways of the diabetes and obesity binomial to hypertensive disorders of pregnancy. *Legend* There is a confluence of maternal diabetes and obesity in insulin resistance. Hyperinsulinemia, glucose and lipid toxicity products contribute to the imbalance toward inflammation, thrombosis and sympathetic-adrenal activation that exert a main influence on endothelial dysfunction of placental vessels

reduced placental perfusion and meta-inflammation is related to maternal diabetes, obesity, and metabolic syndrome. Some altered pathways, such as tyrosine kinase activation by the insulin receptor, persist at the postpartum. The ratio of the anti-angiogenic factor, soluble fms-like tyrosin kinase 1, to placental growth factor in pregnancy has been associated with postpartum hypertension in women with clinical or, possibly, subclinical HDP. Antepartum obesity and diabetes have been linked to this altered upstream [20]. Overall, women with insulin resistance prior to pregnancy develop HDP more frequently than insulin-sensitive women. Insulin resistance is partly explained by risk factors of HDP and has an independent effect per se. Diverse theories of disease suggest that HDP may be caused by cardiovascular disease being occult before pregnancy or may be triggered by GDM development within pregnancy [16].

Gestational hypertension is considered to be a complication less severe than preeclampsia, although this concept is changing toward two stages of a single disease. A common pathophysiology combines the necessary placental involvement and a cluster of predisposing factors. The development of gestational hypertension and preeclampsia seems to be influenced by maternal age, ethnicity, chronic arterial hypertension, smoking, pre-pregnancy BMI, presence of diabetes of any type, glycemic control, and gestational weight gain [1, 4, 7, 10]. The trigger of HDP remains a mystery, but the concurrence of these factors may influence the development of early or late HDP. In GDM, there is an influence of glycemic control [4, 7] and gestational weight gain regardless pre-pregnancy BMI [3, 7] (Table 15.1). However, the strength of these associations is progressively increased by BMI categories of overweight and obesity [7, 11] (Fig. 15.2).

The risk of gestational hypertension [5] and preeclampsia [6] is lowered by intensive treatment of GDM. This may be due to an improved glycemic and weight control. Stringent glycemic control and limited gestational weight gain in obese women were related to a reduced risk of preeclampsia in a randomized trial [6]. The effect of pre-pregnancy BMI per se in Spanish population was evaluated by Ricart et al. [11]. There was an independent influence of BMI and GDM diagnosis that was increased by categories of overweight and obesity. These results were in line with those obtained in a multiethnic population from North America evaluated for preeclampsia risk by BMI and presence of mild GDM. Preeclampsia risk was around 1.7 and 2.0 increased for BMI and GDM respectively,

Table 15.1 Glucose and weight effects on hypertensive disorders in a population of 2037 women with gestational diabetes

Factor	Factor present adjusted OR[a] (95% CI)	Factor absent	*P* value	ARe%[b] (95% CI)
HbA1c[1] $\geq$ 5.9%	2.52 (1.12–5.69)	1.00 (ref)	0.026	60.3 (10.7–82.4)
Pre-pregnancy overweight[2]	2.06 (1.11–3.83)	1.00 (ref)	0.022	51.5 (9.9–73.9)
Pre-pregnancy obesity[3]	8.94 (4.98–16.04)	1.00 (ref)	0.000	88.8 (79.9–93.8)
Excess gestational weight gain[4]	1.91 (1.08–3.37)	1.00 (ref)	0.025	47.6 (7.4–70.3)

Stepwise multiple logistic regression: glucose- and/or weight-related risk factors of pregnancy-induced hypertensive disorders in 2037 women with gestational diabetes. *CI* denotes confidence interval, and *ref* reference. Statistical significance if $P < 0.05$

[a]Odds ratio adjusted for maternal age, tobacco consumption, parity, chronic arterial hypertension, urinary tract infection and gestational age at deliveries

[b]Attributable risk percentage in women exposed to the factor

[1]Averaged 3rd trimester glycated hemoglobin A1c

[2]Pre-pregnancy body mass index (BMI) 25–29.9 kg/m^2

[3]Pre-pregnancy BMI $\geq$ 30 kg/m^2

[4]Above recommendations of *Institute of Medicine* guidelines (2009). Reproduced with permission from Diabetes Metab. 2014;40:204–10. doi:10.1016/j.diabet.2013.12.011

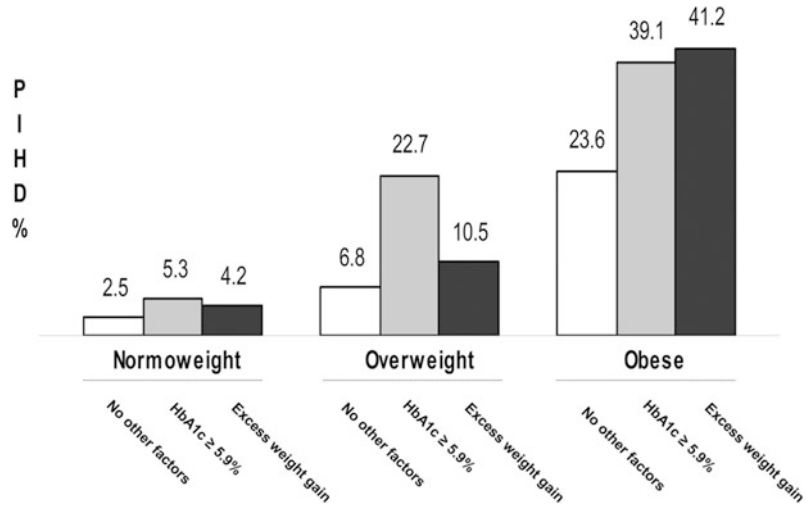


Fig. 15.2 Pregnancy-induced hypertensive disorders by weight categories, weight gain and glycemic control in women with gestational diabetes. *Legend* Prevalence of pregnancy-induced hypertensive disorders (PIHD%) in 2037 women with gestational diabetes grouped by pre-pregnancy body mass index. PIHD% in women with average 3rd trimester glycated hemoglobin (HbA1c) $\geq$ 5.9%, and with excessive gestational weight gain, are shown within categories of normoweight, overweight and obese pre-pregnancy. Reproduced with permission from Diabetes Metab. 2014;40:204–10. doi:10.1016/j.diabet.2013.12.011. Copyright © 2014 published by Elsevier Masson SAS, all rights reserved

and multiplied to around 3.6 when obesity and GDM were combined [21]. In accordance with these data, the prevalence of preeclampsia ranges widely between 1.4–11% and the higher rates are described in populations with GDM and the highest grade of obesity [4].

Diagnosis of Hypertensive Disorders of Pregnancy

HDP entail important risks for adverse pregnancy outcomes. The most severe forms lead to eclampsia, kidney failure and/or stroke in the mother and risk for maternal and neonatal death. More frequently, HDP is accompanied by instrumental delivery or cesarean, indicated preterm delivery below 37 or 34 weeks and small for gestational age birthweight or intrauterine growth restriction. Preeclampsia is a risk factor for cardiovascular disease and stroke in women. In women with GDM, preeclampsia is indicative of diabetes and diabetes complications development [16].

The triage of women at risk of this frequent disorder remains a challenge. Taking a detailed clinical record remains the optimal screening strategy [22]. A combination of serum angiogenic and anti-angiogenic growth factors or the finding or podocytes in the urine are promising. Measurement of resistance to flow of the uterine artery by Doppler ultrasonography has a high negative predictive value among women with history of preeclampsia in a prior gestation. Treatment with aspirin, calcium supplementation, or control of chronic hypertension or diabetes may reduce the incidence or severity of preeclampsia in high-risk women. In this regard, supplementation with vitamins C, E, and D is not recommended for reducing the risk of preeclampsia [15, 23, 24].

Diagnosis of gestational hypertension is defined by new onset hypertension and preeclampsia if accompanied by proteinuria or organ dysfunction in the second half of pregnancy (Table 15.2). Measurements of blood pressure (BP) $\geq$ 140 mmHg systolic or $\geq$90 mmHg diastolic should be confirmed at least once. In women with chronic hypertension, preeclampsia is a confirmed increment of BP $\geq$ 30 mmHg systolic or $\geq$15 mmHg diastolic. Proteinuria is defined as 300 mg of protein on

Table 15.2 Classification of hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy	Diagnosis
Gestational hypertension	>20th gestational week, SBP[2] $\geq$ 140 mmHg or DBP[3] $\geq$ 90 mmHg, resolves within 42 days postpartum
Preeclampsia	>20th gestational week, SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, proteinuria $\geq$ 300 mg/day or organ dysfunction

Preeclampsia is defined as severe preeclampsia if there are signs of organ compromise or arterial hypertension $\geq$160 mmHg systolic or $\geq$110 mmHg diastolic

Table 15.3 Recommendations for weight gain during pregnancy

Prepregnacy BMI[1]	BMI	Total weigh gain, kg, range
Underweight	<18.5	12.7–18
Normal weight	18.5–24.9	11.5–16
Overweight	25–29.9	7–11
Obese	$\geq$30	5–9

As defined by *Institute of Medicine* guidelines (2009)

24-h collection [15]. A quantification of 150 mg on a 12-h sample has shown to be a valid and practical estimate of the 24-h proteinuria [25]. With or without proteinuria, organ dysfunction may be manifested as oliguria, elevated creatinine, elevated transaminases, thrombocytopenia (<100,000 platelet count/μl), epigastric or right upper quadrant abdominal pain, dyspnea, headache, photopsias or impaired vision, seizures, paresis and/or vomiting. These signs of organ compromise or arterial hypertension $\geq$ 160 mmHg systolic or $\geq$110 mmHg diastolic are indicative of severe preeclampsia.

Treatment of Hypertensive Disorders of Pregnancy

Treatment of predisposing conditions may prevent the development of HDP. Management of obesity would be timely before pregnancy. Control of gestational weight gain may help to prevent HDP. Total weight gain of 5–9 kg is recommended for obesity, 7–11.5 kg for overweight and 11.5–16 kg for normal weight women [26] (Table 15.3). Added to these weight gain limits, a risk of preeclampsia was reported in GDM women for linear, every 1-lb/week, increase in weight gain [27]. An alternative objective below 0.6 lb or 270 g per week may be suitable for obese women [12]. Glycemic control of GDM adds an influence. Mean glycemia [4] below 95 mg/dl and/or average glycated hemoglobin levels [7] below 5.9% may be an adequate target to prevent HDP.

GDM intensive treatment resulted in reduced rates of HDP in randomized trials [5, 6]. Nutrition remains a crucial therapy to manage glycemic and weight gain control of GDM women. Diet recommendations are individualized by pre-pregnancy BMI, level of physical activity and rate of gestational weight gain. Caloric content ranges 24–40 kcal/kg/d. Fiber 20–30 g and the following micronutrients intake: sodium 2–3 g/d, calcium 1200 mg/d, iron 30 mg/d and 0.4–1 mg/d are recommended as to low risk pregnant women. The scheme of macronutrients proportion include 50–55% carbohydrates, 15% protein and 25–30% of lipids with a reduction of saturated fat <10%. A number of three main and six total daily intakes is a suggested structure. Sweetened beverages, processed meats, sweets, or meals and snacks are not recommended. Complex carbohydrates, olive oil, and simple cooking (steamed, stewed, grilled, papillote or roasted) are preferred. In addition, the practice of physical activity is a key element of GDM treatment that facilitates glycemic and weight control. Women are encouraged to practice regular activity, preferably of aerobic resistance, 30–60′

for five to seven days a week ideally, at moderate intensity (3–6 METs/h). Insulin therapy is initiated in women with elevated glycemias that persist after diet and physical activity treatment [8].

Pharmacological treatment of HDP in GDM is similar to that in normotolerant women. Elective drugs include those with no adverse effects in offspring and a minimum influence on uterine blood flow. Alphamethyldopa, a central 2-alpha agonist, is the first line therapy due to wide experience in pregnancy and absence of fetal side effects. The beta-blocker labetalol or the calcium channel blockers nifedipine or diltiazem are elective if combination treatment is needed. Precautions include the contraindication of labetalol in asthmatic women and the possible tocolytic effect of calcium channel blockers. The beta-blocker atenolol is not indicated in pregnancy due to its association with intrauterine growth restriction and impaired uterine and placental hemodynamics. Hydralazine, clonidine and prazosin are second line drugs considered to be secure in pregnant women. Diuretics may reduce the uterine-placental flow volume but may be added in uncontrolled HDP or maintained in women with chronic and severe hypertension and/or proteinuria prior to pregnancy. ACE inhibitors or angiotensin receptor blockers are contraindicated in pregnant or women who want pregnancy because of associated teratogenesis [8]. Prevention of preeclampsia with low-dose (75 mg) acetylsalicylic acid before 16 weeks is advisable in high-risk women including those with previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or related autoimmune disease [23]. Calcium supplementation (1.5–2 g/d) is recommended in women with a low intake of calcium in diet [24].

Postpartum of Pregnancy-Induced Hypertensive Disorders

Several studies in women with GDM have shown that insulin resistance persists higher than in nondiabetic control at the postpartum period despite similar levels of insulin [28, 29]. These studies suggest an important and chronic defect in β cell function that is present before and after pregnancy. Thus, development of GDM represents a risk factor for future type 2 diabetes. There is also an associated risk for metabolic syndrome and cardiovascular disease. Cumulative incidence of type 2 diabetes is markedly high in the first 5 years after delivery and appears to plateau after ten years. In 1512 Spanish women with GDM, we found a prevalence of postpartum metabolic syndrome of 10.9%. The three most common features of metabolic syndrome were low levels of high-density lipoprotein cholesterol (31.2%), high fasting glucose values (23.5%), and a high waist circumference (22.8%). The main predictors of metabolic syndrome were overweight or obesity prepregnancy and high antenatal fasting glycaemia [30].

Recent studies have demonstrated that women who developed HDP have an increased risk of cardiovascular complications in later life including stroke, ischemic heart disease, chronic hypertension and chronic kidney disease. The relative risk may range between 2.3 and 3.7 compared to normotensive women [31, 32]. Predictors of chronic hypertension after HDP include a high BMI and multiple previous pregnancies [33]. Similarly, a meta-analysis demonstrated that women with preeclampsia have higher rates of chronic hypertension (relative risk [RR], 3.7; 95% confidence interval [CI], 2.7–5.1) and type 2 diabetes (hazard ratio [HR], 1.8; 95% CI, 1.3–2.6) by an average of 10 years postpartum [13]. In a study of 22,265 ever-pregnant women in Netherlands, those with a history of HDP reported diagnosis of hypertension 7.7 years earlier and women with GDM reported diagnosis of type 2 diabetes mellitus 7.7 years earlier than women without pregnancy complications [34].

The increment of cardiovascular risk is associated with persistent markers of cardiovascular disease after delivery such as microalbuminuria, serum uric acid, carotid intima-media thickness and ultrasound-measured flow-mediated dilation. This suggests a persistent endothelial dysfunction even after resolution of elevated BP. Inversely, preeclampsia is recognized as a risk factor for future diabetes. This effect is evident even when women who had preeclampsia and GDM are excluded. When considering both pregnancy conditions the risk of developing diabetes is moderately increased

in women who had preeclampsia (without GDM), greatly elevated in women who had GDM (without preeclampsia), and highest in women who had both preeclampsia and GDM. The occurrence of both GDM and hypertension or preeclampsia can drastically increase women's chances of developing type 2 diabetes, as much as 13 times the risk, within two decades postpartum [35].

It is clear that these women benefit from regular monitoring to prevent, detect and treat complications after pregnancy. A retrospective cohort study of 1,010,068 pregnant women in Canada reported that the number of women that would need to be followed for five years to detect one case of diabetes was 123 for preeclampsia, 68 for GDM, and 31 for preeclampsia and GDM [36]. The American Diabetes Association [37] recommends screening for persistent diabetes or prediabetes at 6–12 weeks postpartum with 75 g oral glucose tolerance test (OGTT) (Table 15.4). Women should be re-evaluated every three years if the result of this test is found to be normal; however, if impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) is detected they should be screened annually. Although multiple clinical guidelines highlight the importance of screening in these high-risk women, less than half of them are evaluated after delivery. Similarly, American Heart Association [38] has included HDP of pregnancy as a major risk factor for cardiovascular disease.

Large epidemiological studies show that weight loss, increased physical activity and low-fat diets improve insulin sensitivity and lessen the risk of diabetes [39]. Ideally, lifestyle intervention should start during pregnancy and continue postpartum. Women with previous HDP may also benefit from these lifestyle patterns. The goal is to help women return to their prepregnancy weight, if it was normal, or achieve a 5% reduction from prepregnancy weight if overweight. Thus, strategies to help postpartum women overcome barriers to increasing physical activity are needed. A meta-analysis found that lifestyle interventions after preeclampsia could decrease cardiovascular risk by 4–13%; this modest effect may be partially explained by the short follow-up periods of several studies [14]. Another meta-analysis of 18 studies (8712 women) showed that dietary interventions including fiber, dietary fiber, polyunsaturated fatty acids and fish oil had a 33% reduced risk of preeclampsia, but the effect is unknown at postpartum long term [40].

Breastfeeding for 3 months or longer has been associated with lower postpartum weight retention [41], probably because it increases energy expenditure by 15–25% compared with non-breastfeeding mothers. Moreover, lactation seems to reduce the risk of developing postpartum glucose intolerance; reduce long-term obesity risk and prevalence of metabolic syndrome. Further, a study of 379 women with a history of HDP, focusing on lactation, found that breastfeeding was associated with lower postpartum BP among overweight women who developed gestational hypertension but not among women who developed preeclampsia [42].

The total recommended calorie intake for non-breastfeeding women is about 25 kcal/kg per day and for breast-feeding women is 27–30 kcal/kg per day. Women who developed GDM and/or HDP are encouraged to reduce intake of dietary calories and fat and to replace saturated fat with polyunsaturated fat. Moreover, dietary fiber and whole grain food intake is recommended because these nutrients improve insulin sensitivity. In a randomized controlled trial of 260 women with prior GDM, Mediterranean lifestyle intervention group (42.8%) developed fewer glucose disorders at the end of the 3-year follow-up period compared with the control group (56.7%). Dietary recommendations included: high consumption of fruits, vegetables, legumes, nuts; daily use of virgin olive oil;

Table 15.4 Diagnostic criteria for postpartum glucose metabolism disorder

Test	Normal	IFG/IGT	Diabetes
Fasting plasma glucose	<100 mg/dl (<5.6 mmol/L)	100–125 mg/dl (5.6–6.9 mmol/L)	126 mg/dl (7 mmol/L)
75 g-2 h OGTT	140 mg/dl (7.7 mmol/L)	141–199 mg/dl (7.8–11 mmol/L)	200 mg/dl (11.1 mmol/L)

Diagnosis is based on glycemic levels after a 75 g glucose overload. *OGTT* oral glucose tolerance test; *IFG* impaired fasting glucose; *IGT* impaired glucose tolerance

low consumption of red and processed meats; at least 3 serving per week of oily fish and low consumption of non-skimmed dairy products [43]. Physical activity training is well-established prevention strategy for patient with pre-diabetes. Regular physical activity up to 150 min/wk with moderate intensity physical activity is indicated in order to prevent type 2 diabetes, chronic hypertension and, possibly, eventual cardiovascular disease.

Postpartum recommendations in women with GDM and HDP
• Encourage healthy nutrition
• Regular physical activity (150 min/wk)
• Encourage breastfeeding
• Monitor blood pressure, weight, cholesterol and lipoprotein levels
• Perform 75 g-2 h OGTT at 6–12 weeks after delivery

Metformin is less effective than lifestyle modification in preventing the development of type 2 diabetes. However, metformin was more effective than placebo in reducing progression to diabetes during a 10-year follow-up period in women with a history of GDM in Diabetes Prevention Program Outcomes Study [39]. The American Diabetes Association recommends preventive treatment with metformin in patients at high risk of developing diabetes, for example, women with a history of gestational diabetes, very obese individuals and those with severe or progressive hyperglycaemia [44].

Regarding BP, it should be measured during the time of peak postpartum BP at days three to six after delivery. In women with preeclampsia, there is a decrease in BP within 48 h, but BP increases again between 3 and 6 days postpartum. The onset of this BP rise usually coincides with mobilization of extracellular fluid and expansion of intravascular volume [45].

The goal of medical management during immediate postpartum period is to maintain BP levels less than 150/100 mmHg. For women with evidence of end-organ damage, such as kidney disease, diabetes and cardiac disease, BP goals are systolic BP less than 140 mmHg and diastolic BP less than 90 mmHg. Lower BP targets (130/80 mmHg) should be considered in women with albuminuria. Antihypertensive agents generally acceptable for use in breastfeeding include nifedipine, labetalol, methyldopa, captopril and enalapril. Methyldopa and calcium channel blocking agents have the lowest concentration in breast milk. Nonsteroidal anti-inflammatory drugs for analgesia should be used with caution postpartum in women with preeclampsia because these may contribute to postpartum hypertension and labile BP [46].

For women who develop chronic hypertension, we recommend a diet low in salt (5–6 g/day), high in fruits and vegetables, and smoking cessation alike hypertension management outside pregnancy. Finally, it is advisable to provide clinics designed for postpartum care and structured cardiovascular programs in order to identify risk, prevent and treat diabetes, hypertension and cardiovascular disease at its earlier stage. The first step is to address the long-term risk of cardiovascular disease as part of the postpartum care of women with HDP or GDM.

Conclusions

- The risk of gestational hypertension and preeclampsia is reduced by intensive treatment of GDM and, probably, by treatment of obesity prior to pregnancy and by adherence to weight gain guidelines within pregnancy.
- To quit smoking is recommended in all pregnant women, and to perform an early screening of chronic hypertension and diabetes in those being obese, in order to decrease HDP development or severity.

- Diet and physical activity are the basis of a good glycemic and weight control in women with GDM. Insulin treatment is added if needed to achieve an optimal glycemic control.
- The suggested proportion of dietary macronutrients include complex carbohydrates 50–55%, high value protein 15% and total fat below 30% with saturated fat below 10% of the daily intake.
- Women are encouraged to practice regular physical activity at a moderate intensity ideally before pregnancy, in pregnancy and after delivery.
- Drugs methyldopa, labetalol and nifedipine or diltiazem are elective for treatment of chronic hypertension and HDP due to nonassociations with congenital malformations or depletion of the placental blood flow.
- Maintenance of lifestyle modifications is important to lower the cardiometabolic risk at the early or late postpartum of women with GDM and PIHD.

Recommendations and Guidelines

- Clinicians can anticipate HDP by assessing clinical risk factors such as history of chronic hypertension, smoking, pre-pregnancy obesity, excessive gestational weight gain, diabetes and poor glycemic control.
- The risk of HDP is lowered by intensive treatment of gestational diabetes and by control of gestational weight gain.
- Diagnosis of gestational hypertension is defined by new onset blood pressure (BP) ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic confirmed in the second half of pregnancy. Preeclampsia is diagnosed if accompanied by proteinuria or organ dysfunction.
- Treatment of HDP include drugs with no fetal adverse effects and a minimum effect on utero-placental flow. Alphamethyldopa, labetalol and nifedipine or diltiazem are first line therapy.
- HDP may persist in the shape of insulin resistance at the postpartum. Treatment of obesity before pregnancy would be timely to prevent HDP and postpartum metabolic syndrome.

References

1. Goldman M, Kitzmiller JL, Abrams B, Cowan RM, Laros RK. Obstetric complications with GDM. Effects of maternal weight. Diabetes. 1991;40(Suppl 2):79–82.
2. Beucher G, Viaris de Lesegno B, Dreyfus M. Maternal outcome of gestational diabetes mellitus. Diabetes Metab. 2010;36:522–37.
3. Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. Diabetes Endocrine Pregnancy Outcome Study in Toronto. QJM. 2001;94:347–56.
4. Yogev Y, Xenakis EMJ, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. Am J Obstet Gynecol. 2004;191:1655–60.
5. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477–86.
6. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361:1339–48.
7. Barquiel B, Herranz L, Grande C, Castro-Dufourny I, Llaro M, Parra P, et al. Body weight, weight gain and hyperglycaemia are associated with hypertensive disorders of pregnancy in women with gestational diabetes. Diabetes Metab. 2014;40:204–10.
8. Pallardo LF, Bartha JL, Herranz L, editors. Diabetes y embarazo. 4th ed. Barcelona: EdikaMed; 2015 (Spanish).
9. Acién Álvarez P. Tratado de Obstetricia y Ginecología. Obstetricia. Alicante (Spain): Molloy Editors; 1998 (Spanish).

10. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330:565.
11. Ricart W, López J, Mozas J, Pericot A, Sancho MA, González N, et al. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. Diabetologia. 2005;48:1736–42.
12. Scifres C, Feghali M, Althouse AD, Caritis S, Catov J. Adverse outcomes and potential targets for intervention in gestational diabetes and obesity. Obstet Gynecol. 2015;126:316–25.
13. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335:974.
14. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EAP, Habbema JDF. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG. 2013;120:924–31.
15. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
16. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Curr Diab Rep. 2015;15:9.
17. Roberts R. Hypertension in women with gestational diabetes. Diabetes Care. 1998;21(Suppl 2):B27–32.
18. Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M, Fontaine P. Pregnancy induced hypertension in women with gestational carbohydrate intolerance: the diagest study. Eur J Obstet Gynecol Reprod Biol. 2002;102:31–5.
19. Fisher SJ. Why is placentation abnormal in preeclampsia? Am J Obstet Gynecol. 2015;213:S115–22.
20. Goel A, Maski MR, Bajracharya S, Wenger JB, Zhang D, Salahuddin S, et al. Epidemiology and mechanisms of De Novo and persistent hypertension in the postpartum period. Circulation. 2015;132:1726–33.
21. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012;35:780–6.
22. American College of Obstetricians and Gynecologists. Committee Opinion No. 638: First-Trimester Risk Assessment for Early-Onset Preeclampsia. Obstet Gynecol 2015;126:e25–7.
23. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2007;CD004659.
24. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2010;CD001059.
25. Stout MJ, Conner SN, Colditz GA, Macones GA, Tuuli MG. The utility of 12-hour urine collection for the diagnosis of preeclampsia: a systematic review and meta-analysis. Obstet Gynecol. 2015;126:731–6.
26. Rasmussen KM, Catalano PM, Yaktine AL. New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. Curr Opin Obstet Gynecol. 2009;21:521–6.
27. Harper LM, Tita A, Biggio JR. The institute of medicine guidelines for gestational weight gain after a diagnosis of gestational diabetes and pregnancy outcomes. Am J Perinatol. 2015;32:239–46.
28. Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. J Clin Endocrinol Metab. 2001;86:568–73.
29. Kautzky-Willer A, Prager R, Waldhausl W, Pacini G, Thomaseth K, Wagner OF, et al. Pronounced insulin resistance and inadequate beta-cell secretion characterize lean gestational diabetes during and after pregnancy. Diabetes Care. 1997;20:1717–23.
30. Barquiel B, Herranz L, Hillman N, Burgos MÁ, Pallardo LF. Prepregnancy body mass index and prenatal fasting glucose are effective predictors of early postpartum metabolic syndrome in Spanish mothers with gestational diabetes. Metab Syndr Relat Disord. 2014;12:457–63.
31. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol. 2009;114:961–70.
32. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, et al. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010;28:826–33.
33. Shopen N, Schiff E, Koren-Morag N, Grossman E. Factors that predict the development of hypertension in women with pregnancy-induced hypertension. Am J Hypertens. 2016;29:141–6.
34. Heida KY, Franx A, van Rijn BB, Eijkemans MJC, Boer JMA, Verschuren MWM, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. Hypertension. 2015;66:1116–22.
35. Engeland A, Bjørge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. Eur J Epidemiol. 2011;26:157–63.
36. Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, et al. Preeclampsia as a risk factor for diabetes: a population-based cohort study. PLoS Med. 2013;10:e1001425.
37. American Diabetes Association. Management of diabetes in pregnancy. Diabetes Care. 2015;39:S94–8.

38. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the american heart association. Circulation. 2011;123:1243–62.
39. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100:1646–53.
40. Allen R, Rogozinska E, Sivarajasingam P, Khan KS, Thangaratinam S. Effect of diet- and lifestyle-based metabolic risk-modifying interventions on preeclampsia: a meta-analysis. Acta Obstet Gynecol Scand. 2014;93:973–85.
41. Østbye T, Krause KM, Swamy GK, Lovelady CA. Effect of breastfeeding on weight retention from one pregnancy to the next: results from the North Carolina WIC program. Prev Med (Baltim). 2010;51:368–72.
42. Countouris ME, Schwarz EB, Rossiter BC, Althouse AD, Berlacher KL, Jeyabalan A, et al. Effects of lactation on postpartum blood pressure among women with gestational hypertension and preeclampsia. Am J Obstet Gynecol 2016.
43. Pérez-Ferre N, Del Valle L, Torrejón MJ, Barca I, Calvo MI, Matía P, et al. Diabetes mellitus and abnormal glucose tolerance development after gestational diabetes: a three-year, prospective, randomized, clinical-based, Mediterranean lifestyle interventional study with parallel groups. Clin Nutr. 2015;34:579–85.
44. American Diabetes Association. Prevention or delay of type 2 diabetes. Diabetes Care. 2015;39:S36–8.
45. Ferrazzani S, De Carolis S, Pomini F, Testa AC, Mastromarino C, Caruso A. The duration of hypertension in the puerperium of preeclamptic women: relationship with renal impairment and week of delivery. Am J Obstet Gynecol. 1994;171:506–12.
46. Makris A, Thornton C, Hennessy A. Postpartum hypertension and nonsteroidal analgesia. Am J Obstet Gynecol. 2004;190:577–8.

Chapter 16
Links Between Polycystic Ovary Syndrome and Gestational Diabetes Mellitus

Anastasia Trouva and Evanthia Diamanti Kandarakis

Key Points

- Polycystic ovary syndrome and gestational diabetes mellitus are both prevalent during the reproductive life of a woman, affecting negatively the pregnancy course as well as the future life of the mother and offspring, making the two conditions a challenge for endocrinologists and obstetricians.
- The diagnostic approach of both polycystic ovary syndrome and gestational diabetes has been widely debated and their prevalence estimation depends on the criteria used for the diagnosis.
- Insulin resistance is the pathogenetic mechanism that links the two conditions.
- Gestational diabetes mellitus is the most common pregnancy complication of polycystic ovary syndrome but several other complications and risks interweave the two conditions. Metabolic syndrome and type 2 diabetes are the most serious long-term consequences of both polycystic ovary syndrome and gestational diabetes.
- Specific treatment strategies apply to both entities, with life-style modification being the cornerstone of the therapeutic approach as it targets the pathophysiology of polycystic ovary syndrome and gestational diabetes. Metformin is the only pharmacological agent that has a wide potential in the management of both conditions targeting multiple aspects of polycystic ovary syndrome and gestational diabetes mellitus.

Keywords Polycystic ovary syndrome · Gestational diabetes mellitus · Insulin resistance · Metabolic syndrome · Life style modification · Metformin

A. Trouva (✉)
Department of Molecular Medicine and Surgery, Karolinska Institutet,
Solna, Sweden
e-mail: anastasia.trouva@ki.se

A. Trouva
Center for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden

E. Diamanti Kandarakis
Department of Endocrinology and Center of Excellence in Diabetes and Metabolic Diseases,
Athens Euroclinic, University of Athens Medical School, Athens, Greece
e-mail: e.diamanti.kandarakis@gmail.com

E. Diamanti Kandarakis
Department of Endocrinology and Diabetes Center of Excellence, EUROCLINIC,
9 Athanasiadou Str, 11521 Athens, Greece

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_16

Abbreviations

ADA	American diabetes association
AE	Androgen excess
AGEs	Advanced glycation end products
ASRM	American society for reproductive medicine
BMI	Body mass index
BPA	Bisphenol A
CS	Caesarean section
DHEAS	Dehydroepiandrosterone sulphate
DIP	Diabetes in pregnancy
EASD	European association for the study of diabetes
ESHRE	European society of human reproduction and embryology
FSH	Follicle-stimulating hormone
GDM	Gestational diabetes mellitus
GnRH	Gonadotropin-releasing hormone
HAPO	Hyperglycemia and adverse pregnancy outcome
hPL	Human placental lactogen
IADPSG	International association of the diabetes and pregnancy study groups
ICAM	Intercellular adhesion molecule
IFNγ	Interferon gamma
IL-6	Interleucin-6
IOM	Institute of medicine
Kcal	Kilocalories
Kg	Kilos
LH	Luteinizing hormone
LGA	Large for gestational age
MiG	Metformin in gestation (trial)
Min	Minutes
NAFLD	Non-alcoholic fatty liver disease
NICU	Neonatal intensive care unit
NIH	National Institute of Health
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
PE	Preeclampsia
RCT	Randomized controlled trial
SHBG	Sex-hormone binding globulin
TNF	Tumour necrosis factor
VCAM	Vascular cell adhesion molecule
WHO	World health association

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy, affecting up to 10% of women in their reproductive years. The aetiology of PCOS is not clearly elucidated but the clinical significance of the syndrome lies in the fact that PCOS is a major cause of fertility impairment, menstrual and ovulatory irregularity, clinically expressed hyperandrogenism and metabolic imbalance among women. Insulin resistance and hyperinsulinemia have been proposed as the most reasonable pathogenetic mechanisms for PCOS [1].

Gestational diabetes mellitus (GDM) is the onset or first recognition of abnormal glucose tolerance during pregnancy. GDM is clinically important because of its short- and long-term implications affecting the course and the outcome of the pregnancy as well as the future health of the mother and the offspring. GDM may predict a higher cardiovascular risk and type 2 diabetes.

This review aims to explore the inter-relationship between GDM and PCOS since both entities influence women's health at various phases of reproductive and post-reproductive life and have consequences for the health of the offspring as well. Common therapeutic modalities, applying to both conditions because of the interesting links in their pathophysiological mechanisms may alleviate the risk of developing shared long-term consequences.

Definitions/Diagnosis and Epidemiology

An analogy between PCOS and GDM lies in the fact that the definitions of the two entities have generated intense debate among experts in the field.

The definition of PCOS is suggested by three major groups [2–4] which are all based on consensus (Table 16.1). However, the main characteristic of the syndrome, which is clinical and/or biochemical hyperandrogenism with ovulatory dysfunction excluding other hyperandrogenemic abnormalities, remains the common denominator of the diagnostic approach in women all around the world.

The most commonly used criteria in clinical practice are the Rotterdam criteria, which require two out of three of the following: oligo-ovulation or anovulation, clinical or biochemical signs of androgen excess and ultrasonographic polycystic ovary morphology [2]. Other causes of hyperandrogenism must also be excluded.

Four different phenotypes of PCOS are identified by using the possible combinations of these criteria [5]:

- Type A: hyperandrogenism, chronic anovulation and polycystic ovaries
- Type B: hyperandrogenism and chronic anovulation
- Type C: hyperandrogenism and polycystic ovaries
- Type D: chronic anovulation and polycystic ovaries

Globally, in different populations and unselected women, the prevalence of PCOS has been reported quite uniform, ranging from 6 to 10% [6–8] with few exceptions. Ethnic variations in PCOS seem to be greatly determined by the genetic background in humans [9].

On the other hand, GDM is defined as a glucose intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy [10].

Table 16.1 Definitions of PCOS according to available criteria

Rotterdam-2003 (ESHRE/ASRM) (most frequently used)	AE and PCOS Society-2009	NIH-1990
≥2 of the following: • Chronic oligo- or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovaries on ultrasound	Both the criteria below: • Hyperandrogenism: hirsutism and/or hyperandrogenemia • Ovarian dysfunction: oligo-anovulation and/or polycystic ovaries on ultrasound	Both the criteria below: • Chronic anovulation • Clinical and/or biochemical hyperandrogenism
Common to all criteria: *Exclusion of other hyperandrogenic disorders*		

Legend The definition of PCOS is suggested by three major groups but the Rotterdam criteria are the most commonly used

International consensus is still lacking for screening methods and classification of GDM [11]. In 2010 the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended new criteria for diagnosing GDM [12] based on the results of the "Hyperglycemia and Adverse Pregnancy Outcome" (HAPO) study and the risk of adverse pregnancy outcomes. The IADPSG criteria were adopted by the World Health Organization (WHO) in 2013 [13] and American Diabetes Association (ADA) in 2014 [14]. A 2-h 75 g Oral Glucose Tolerance Test (OGTT) at 24–28 week of gestation is now recommended as the diagnostic tool by the European Association for the Study of Diabetes (EASD), IADPSG, ADA and WHO. Earlier testing may be performed based on parameters of high risk such as pre-pregnancy adiposity, history of diabetes in first degree relatives, previous history of GDM or large for gestational age (LGA) babies, diagnosis of PCOS, high maternal age, glycosuria or belonging to an ethnic group having high prevalence of GDM, and then repeated at 24–28 weeks of gestation, if a negative result is obtained at the earlier testing time point (Fig. 16.1). The cut-off values for a positive test are shown in Table 16.2. The difference from IADPSG recommendations is that the new WHO guidelines set a range of plasma glucose levels to differentiate diabetes in pregnancy (regarded as diabetes existing prior to pregnancy) from GDM, which is necessary because of the rising prevalence of type 2 diabetes in younger ages [15].

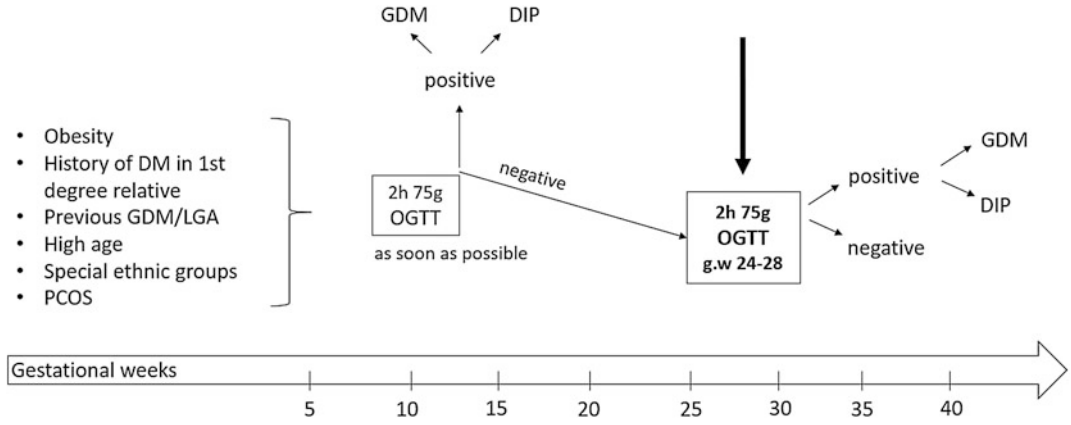


Fig. 16.1 Flow-chart for the diagnosis of GDM. The "gold-standard" for the diagnosis of diabetes during pregnancy is a 2 h 75 g OGTT at 24–28 gestational week. Earlier testing should be performed in case of relevant risk-factors, with a negative test leading to new OGTT in gestational week 24–28. *OGTT* oral glucose tolerance test, *DIP* diabetes in pregnancy, *GDM* gestational diabetes mellitus

Table 16.2 Criteria for diagnosis of gestational diabetes mellitus (GDM) and diabetes mellitus in pregnancy with a 2-h oral glucose tolerance test (at any time during pregnancy)

Diagnosis	Fasting plasma glucose	1-h glucose following 75 g oral glucose load	2-h glucose following 75 g oral glucose load
Normal	<5.1 mmol/l (92 mg/dl)	<10 mmol/l (180 mg/dl)	<8.5 mmol/l (153 mg/dl)
GDM	5.1–6.9 mmol/l (92–125 mg/dl)	≥ 10 mmol/l (180 mg/dl)	8.5–11.0 mmol/l (153–199 mg/dl)
Diabetes mellitus in pregnancy	≥ 7 mmol/l (126 mg/dl)	*	≥ 11.1 mmol/l (200 mg/dl)

*There are no established criteria for the diagnosis of diabetes based on the 1-h post-load value

The prevalence of GDM is not easily estimated. It varies globally and even within a country's population since it depends on racial and ethnical factors. Furthermore, the prevalence of GDM is affected by the different screening strategies (general or selective), diagnostic criteria and the prevalence of type 2 diabetes in any particular country. Recently two studies evaluated the prevalence of GDM globally [16, 17] which ranged from <5% in countries such as Pakistan, Belgium, Denmark, Estonia, Ireland, South Korea, South Africa and United Kingdom, to <10% in Italy, Turkey, Brazil, United States, Morocco and Australia, to a prevalence higher than 20% in Bermuda and Nepal [18]. Implementation of the new diagnostic criteria is believed to result in increase of GDM prevalence to nearly 18% [19], with tremendous impact on the economy of the health care systems.

To conclude, PCOS and GDM are common conditions during the reproductive age of women and the prevalence of both rises when broader criteria are used for their diagnosis.

Links Between PCOS and GDM in Epidemiology

GDM is the most predominant complication during the pregnancy of women with PCOS and its prevalence among these women has been assessed in different studies (Table 16.3). In the most recent meta-analysis concerning pregnancy complications in women with PCOS, the risk of GDM was found to be approximately threefold higher in women with PCOS compared to controls [20] without, though, adjusting these results for confounders such as BMI. A multicenter randomized controlled trial (RCT) evaluating the potential of metformin to reduce gestational complications among women with PCOS, showed that the incidence of GDM was 17.6 and 16.9% in the metformin and placebo group, respectively [21] and in a large study from Sweden [22] the prevalence of GDM was more than twice higher in pregnant women with PCOS, even when data were adjusted for confounders. In accordance, GDM incidence was almost threefold increased in PCOS patients compared to controls (14.7% vs. 5.3%, respectively) in a recent prospective study from Italy [23]. Finally, de Wilde et al. [24] reported an even higher incidence of GDM of up to 22% in 189 women with PCOS but no comparison with controls without PCOS was done [25].

Even the prevalence of polycystic ovarian morphology was found to be higher in women with a history of GDM [26], in agreement with the findings of a study in Swedish population in which, among women with previous GDM, ultrasonographic, clinical and endocrine signs of polycystic ovary syndrome were much increased [27].

In conclusion, current available data suggest that GDM is more common in women with PCOS compared to general population or to women without the syndrome matched for age and BMI. The choice of PCOS diagnostic criteria or of phenotypic features has important implications on the prevalence of GDM and other pregnancy complications and should be taken into consideration when interpreting the results of studies [28].

Table 16.3 Studies reporting prevalence of gestational diabetes mellitus in subjects with polycystic ovary syndrome

Study	Studied population	GDM prevalence/OR in PCOS versus controls
Qin et al. [20]—review/meta-analysis	4982 women with PCOS (4994 pregnancies) (diagnostic criteria different among studies) 119,692 controls (1,196,775 pregnancies) Multiracial	OR 2.81(95% CI: 1.99–3.98)—all included studies OR 3.58 (95% CI: 3.05–4.20)—borderline eligible studies excluded
Vanky et al. [21]—RCT	274 pregnant women with PCOS (Rotterdam 2003) 136 received metformin (135 analyzed) 138 received placebo (135 analyzed) Caucasian > 96%	WHO (1998): 16.9% in the placebo group
Roos et al. [22]—population based cohort study	3787 women with PCOS (according to ICD-codes) 1,191,336 controls (matched for age, BMI and other confounders) Swedish population, race not specified	OR 2.32 (95% CI: 1.88–2.88)
Palomba et al. [23]—prospective controlled trial	150 non-obese PCOS (Rotterdam-2003) women 150 age- and BMI-matched controls Caucasian	14.7% vs 5.3%; $P = 0.011$
De Wilde et al. [24]—multicentre prospective cohort study	189 pregnant PCOS women (Rotterdam 2003) No controls Dutch population, majority of European descent	ADA (2003), 100 g OGTT: 22% of studied PCOS women

Legend The studies were conducted in adult women unless else stated. The choice of PCOS diagnostic criteria or of phenotypic features affects significantly the estimated prevalence of GDM

Pathogenesis/Pathophysiology

Similarities between the metabolic conditions underlying GDM and PCOS may indicate that common factors are implicated in the etiopathogenesis of the two entities with insulin resistance playing a central role in the linking mechanism [29]. Insulin resistance is a decrease in cellular responsiveness to insulin signalling which leads to increased secretion of insulin, called "compensatory hyperinsulinemia" [30].

Insulin Resistance: The Main Metabolic Disruption in PCOS

PCOS is dominated by three major endocrine disruptions: insulin resistance, hyperinsulinemia and hyperandrogenemia. Insulin has been shown to elevate Gonadotropin-Releasing Hormone (GnRH) and Luteinizing Hormone (LH) secretion in both dose- and time-dependent way [31], which results in increased pulsatile secretion of GnRH and LH with increased LH/FSH ratio, a PCOS finding enhancing the effect of ovarian steroidogenic changes [32]. Furthermore, insulin acts in synergy with LH to increase theca cell androgen production in women with PCOS by activation of a specific signalling pathway via its own receptor [33]. Other factors which are commonly met in women with PCOS act synergistically with insulin in potentiating LH release, such as hyperleptinemia [34] and decreased hypothalamic opioid activity [35]. Another suggested mechanism by which hyperinsulinemia exacerbates androgen signalling is through inhibition of hepatic sex-hormone binding globulin (SHBG) synthesis by insulin, thus increasing the levels of bioavailable androgens [36]. Nevertheless, Selva et al. proposed that this effect is depended on hyperglycemia-mediated

Hepatocyte Nuclear Factor 4-α downregulation and not associated with a direct inhibition of SHBG expression by insulin [37]. Finally, concerning insulin resistance in the ovary, there seem to be a differentiation point; the granulosa cells appear to be resistant to insulin as far as glucose metabolism is concerned but the theca cells appear to be insulin-sensitive and overproduce androgens under both in vitro and in vivo insulin stimulation [1].

Obesity is another condition implicated in the pathogenesis of PCOS. Women having this syndrome are more obese with higher rates of central adiposity compared to controls without PCOS, and weight strongly influences the prevalence and clinical severity of PCOS. Hyperandrogenemia and obesity of PCOS seem to be linked through the following suggested mechanism: testosterone formation by steroidogenic cells is upregulated by insulin and this effect is mediated by a transcription factor involved in adipogenesis [38]. Women with PCOS according to 1990-NIH criteria having hyperandrogenic phenotype are more insulin resistant than anovulatory women with PCOS with normal androgen levels who are relatively healthier metabolically [39, 40]. According to Legro et al. [41] a having a BMI < 27 kg/m^2 significantly alleviates this metabolic risk. This seems to be in accordance with the finding that women with PCOS who are able to maintain normal weight with ageing exhibit a better metabolic profile than those who do not, as showed by Livadas et al. [42].

Apart from insulin resistance and obesity, other factors seem to be involved in the etiopathogenesis of the syndrome. The role of Advanced Glycated End-products (AGEs) has recently been thoroughly studied, since circulating AGEs concentrations are increased, independently of obesity, in women with PCOS [43]. AGEs are products of non-enzymatic glycation and oxidation of proteins from endogenous or exogenous (dietary) sources and are implicated in the pathogenesis of cardiometabolic disturbances, insulin resistance, and possibly, direct ovarian dysfunction [44]. Moreover, other endocrine disruptors like bisphenol A (BPA) are implicated in the pathogenesis of PCOS [45] as well as of obesity, metabolic syndrome and type 2 diabetes [46].

Premature adrenarche has been proposed to be a precipitant and a risk factor both for PCOS and for metabolic syndrome later in life. It has been shown that such individuals carry a 15–20% risk of developing PCOS [47]. Moreover, a higher prevalence of hyperinsulinemia, functional ovarian hyperandrogenemia, dyslipidemia and obesity have also been observed in adolescent girls with premature adrenarche [48], suggesting that premature adrenarche may be linked to metabolic disturbances.

Aggravation of Physiologic Insulin Resistance: The Basis of GDM

Insulin resistance is a physiologic state during pregnancy, mediated by maternal hormones such as progesterone, oestrogen, cortisol and mainly human placental lactogen (hPL) [49], which aim to increase the glucose offer for the fetal metabolism. To sustain euglycemia, the pregnant woman needs to increase her insulin production by 200–250%. GDM manifests when the pregnant woman cannot produce a sufficient insulin response (due to defective or inadequate compensatory mechanisms) to counterbalance the physiologic insulin resistance state induced by pregnancy [18]. Obesity is an important risk factor for GDM. Apart from augmenting the insulin resistance mechanisms described above, obesity is responsible for a systemic inflammatory environment with high levels of Tumour Necrosis Factor (TNF) [50], a cytokine which is associated with insulin resistance. Another important regulator of metabolism homeostasis during pregnancy seems to be adiponectin, which has an insulin-sensitizing activity. Except from adipocytes, where adiponectin is synthesized, placenta is also responsible for its production during gestation. Hypoadiponectinemia is a marker for insulin resistance, present in situations such as obesity, type 2 diabetes and gestational diabetes. Adiponectin is decreased in obesity [51] and decreased levels seem to be an independent predictor of GDM. Other cytokines such as TNF, Interferon gamma (IFNγ), Interleucin-6 (IL-6) and leptin seem to alter

adiponectin and its receptor's levels in women with GDM [29, 52]. GDM manifests both in obese and in lean women but the pathophysiological mechanisms of the disease seem to be different in the two groups.

Clinical Aspects: Common Sequelae

The close relationship of PCOS and GDM becomes evident when it comes to the consequences of the two conditions which stretch during different stages of reproductive and post-reproductive life.

Complications During Pregnancy

PCOS and GDM share common complications during the course of the pregnancy and the perinatal period (Fig. 16.2).

The risk of pregnancy complications is increased in women with PCOS. The spontaneous abortion rate in this group of women is 20–40% higher than in the general obstetrical population [53]. Moreover, a meta-analysis by Qin et al. including 4982 women with PCOS showed that among these women the risk of developing GDM, preeclampsia, preterm birth and caesarean section was significantly higher compared to controls and their babies had a significantly higher risk of admission to the

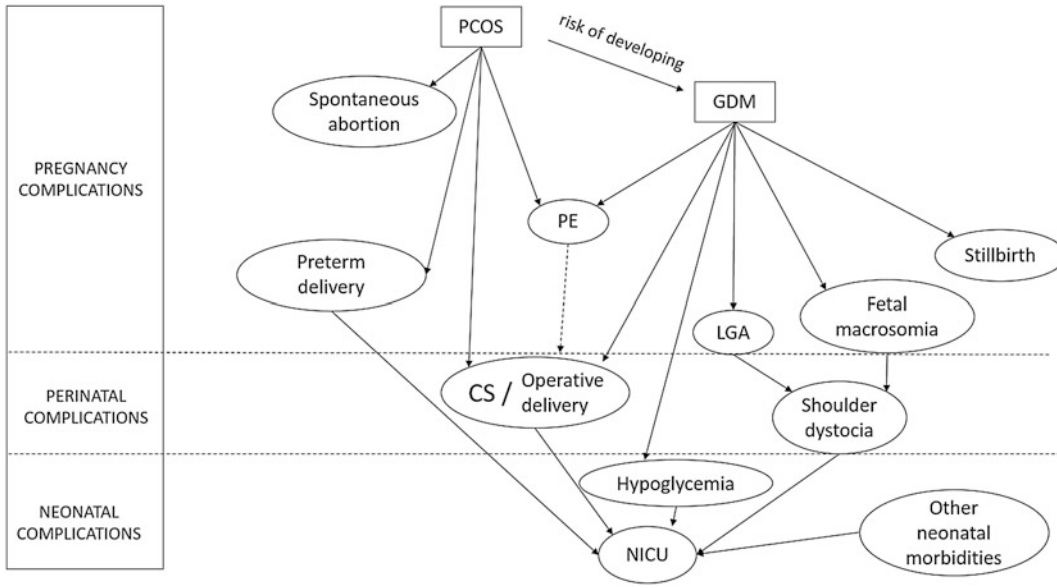


Fig. 16.2 Pregnancy- and perinatal complications of polycystic ovary syndrome and gestational diabetes mellitus. Women with polycystic ovary syndrome (PCOS) have an increased risk of developing gestational diabetes mellitus (GDM). Spontaneous abortion, preeclampsia, preterm delivery are other known complications of PCOS. On the other hand, preeclampsia (PE), stillbirth, fetal macrosomia and LGA neonates as well as delivery with caesarean section (CS) or other operative delivery (often because of shoulder dystocia) are pregnancy/perinatal complications which are linked to GDM. Neonates of GDM mothers can experience hypoglycemia and other comorbidities and need to be admitted to the neonatal intensive care unit (NICU). This diagram shows the various links between the common complications of PCOS and GDM

neonatal intensive care unit (NICU) [20]. Palomba et al. [54] suggested that the low-grade chronic inflammation which is often seen in these patients and is expressed by high levels of C-reactive protein, may be associated with the high risk of adverse pregnancy outcome.

GDM is further linked to several complications during pregnancy. Insulin resistance, the basis of GDM, is associated with the development of preeclampsia, which is occurs in higher rate in women with GDM than in controls [55]. Women with GDM and a poor glycaemic control experience high risk for stillbirth [56]. The most common adverse neonatal outcomes associated with GDM are LGA infants and fetal macrosomia, with maternal hyperglycemia and excessive weight gain augmenting this risk [19, 57]. Macrosomia is, in its turn, related to increased risk of operative delivery and shoulder dystocia [58].

Long-Term Consequences

Metabolic disturbances are common among women with PCOS. Obesity, hyperinsulinemia and insulin resistance independent of obesity are highly prevalent in this group compared to controls [59], and so is non-alcoholic fatty liver disease (NAFLD) [60]. The prevalence of metabolic syndrome appears to be multi-fold increased in women with PCOS, reaching numbers as high as 47% [61]. As a consequence of the above, the risk of developing type 2 diabetes is increased in PCOS, especially in women with a first-degree relative having the disease [62]. The annual conversion rate from normal to impaired glucose tolerance has been estimated to be 16% [63]. Finally, PCOS is associated with dyslipidemia, mainly low high-density lipoprotein cholesterol and high levels of triglycerides and low-density lipoprotein cholesterol [64].

An increased risk of cardiovascular disease in women with PCOS is not yet well established [65]. However, obesity, insulin resistance, impaired glucose tolerance and dyslipidemia which often co-exist with PCOS, may predispose to coronary heart disease. High levels of C-reactive protein, commonly elevated in PCOS subjects, is also a cardiovascular disease-predictor. Finally, several studies have shown the presence of endothelial dysfunction in this group of women [66, 67], which may, in its turn, also predispose to cardiovascular disease.

GDM has as well serious implications for the future health of the mother and is considered to be one of the factors that can well predict the development of type 2 diabetes later in life. As shown in numerous studies, the risk of developing type 2 diabetes mellitus is multi-fold increased among women who have had a pregnancy complicated with GDM compared to women with a euglycemic pregnancy [68] and this risk correlates to the grade of defect in insulin secretion and action that these women seem to have. According to a systematic review of 28 studies, after the index pregnancy, the cumulative incidence of diabetes ranged from 2.6% to over 70% with the highest risk in the first five years and a plateau after 10 years [69]. In a Canadian study, the incidence of type 2 diabetes was more than ninefold increased by nine years in women who have had GDM compared to those that did not (19% compared to 2%) [70].

GDM conveys also a higher risk for the development of metabolic syndrome and cardiovascular disease. In a study by Retnakaran et al. [71], the 3-month postpartum prevalence of metabolic syndrome increased progressively from 10% among women with normoglycemia during pregnancy to 17.6% in women with impaired glucose tolerance during pregnancy, to reach 20% among those with previous GDM. GDM increases the risk of cardiovascular disease by 70%, as showed in a study where women with and without GDM were followed for 11.5 years [72]. This increased risk seems to be mainly attributed to the development of type 2 diabetes and metabolic syndrome [18].

In conclusion, PCOS and GDM appear to be conditions that independently convey a very high risk for the development of metabolic syndrome, type 2 diabetes and possibly endothelial dysfunction and cardiovascular disease later in the woman's life.

Consequences for the Offspring

The intrauterine environment in both PCOS and GDM and its consequences on the offspring have been the subject of several studies.

An important link between PCOS and GDM is elucidated in a study by Boutzios et al. [73], who demonstrated that the oxidative stress markers of PCOS neonates were comparable to those of GDM neonates, as was the metabolic/hormonal profile with similar pattern of hyperandrogenemia and hyperinsulinemia. Thus, the hypothesis that a mother's milieu determines the future health of her offspring was confirmed.

Children of PCOS mothers seem to have increased risk for endocrine and cardiovascular disorders later in life, such as insulin resistance, obesity, hypertension and dyslipidemia [74]. This high risk can be attributed to both genetic and environmental factors. The cardiovascular aberrations could partly be linked to a reduced breastfeeding rate among PCOS-mothers, related to mid-pregnancy hyperandrogenemia [75]. Daughters of women with PCOS may themselves have some characteristics of PCOS before and after puberty, such as increased testosterone levels, hyperinsulinemia and increased ovarian volume [28, 76]. Finally, a very recent population-based study in Sweden found that maternal PCOS increases the odds of Autism Spectrum Disorders in the offspring by 59% and this risk was further increased by the co-existence of maternal obesity and PCOS [77].

In a similar pattern, intrauterine exposure to GDM is associated with obesity and altered glucose metabolism in the offspring [78]. Infants of mothers with GDM are at an increased risk of developing type 2 diabetes later in life. Studies performed in Pima Indians, a population with very high prevalence of GDM, show that 45% of offspring of mothers with GDM develop type 2 diabetes between 20 and 24 years of age compared to 1.4% of the children of non-diabetic mothers, thus proposing that the intrauterine milieu is an important determinant of the development of diabetes in the offspring, in addition to genetic factors [79]. Several reports have shown an association between maternal GDM and elevated risk for Autism Spectrum Disorders in offspring [80] but Xiang et al. [81] could actually identify an association of GDM with offspring autism for GDM diagnosed by 26 weeks' gestation, but not after 26 weeks or in preexisting maternal diabetes.

Table 16.4 summarizes the long-term consequences that are common between PCOS and GDM regarding both the mother and the offspring.

Table 16.4 Long term consequences common between polycystic ovary syndrome and gestational diabetes mellitus

Maternal	In the offspring
High risk for the development of	
Metabolic syndrome	Oxidative stress
Type 2 diabetes mellitus	Hyperinsulinemia
Endothelial dysfunction and cardiovascular disease	Components of the metabolic syndrome

Legend Polycystic ovary syndrome and gestational diabetes mellitus share important consequences both for the mother and the offspring

Guidelines: Common Therapeutic Approaches

Only treatment strategies that can apply in both PCOS and GDM/pregnancy will be reviewed here.

Life-Style Modification

Lifestyle modification is the cornerstone of the treatment of both PCOS and GDM. All other interventions should come as adjuvant treatment modalities.

In case of obesity, improvement of insulin sensitivity via diet- and exercise-induced reduction of weight improves clinical, metabolic and reproductive parameters of PCOS [82] and even a 10% body weight reduction can be sufficient to induce these changes [83]. Anthropometric parameters such as body mass index (BMI), waist circumference and waist to hip ratio decrease with lifestyle interventions and at the same time endocrine parameters improve significantly (serum testosterone levels decrease and SHBG levels increase resulting in lower free androgen index). A systematic review reported that exercise of any form, frequency, or length was associated with improvements in ovulation and insulin sensitivity as well as weight reduction [84]. Studies on the endometrium of obese women with PCOS showed that lifestyle intervention upregulates gene and protein levels of molecules involved in insulin signalling [85] and that it alters, but does not fully restore, oestrogen and androgen receptor expression [86].

Concerning changes in the quality of the diet, it seems that a regimen with 50% of total calories from carbohydrates (preferably with a low glycemic index), 30% from fat (mainly mono- and poly-unsaturated fat, less than 10% from saturated fat), 20% from proteins and fibre-rich is the most suitable for PCOS patients [87]. At the same time, energy restriction by 500–1000 kcal/day, independent of weight reduction, seems to ameliorate insulin resistance and reduce hyperandrogenemia in obese patients with PCOS and should therefore be recommended in this patient group [87].

Not many studies have assessed the outcome of physical activity in patients with PCOS and guidelines are lacking. General recommendations include moderate-intensity aerobic exercise (e.g. vigorous walking) for at least 30 min and for minimum 5 days per week for both obese and non-obese patients. Strenuous-intensity aerobic exercise (e.g. jogging) for at least 20 min and for at least 3 days per week or combinations of moderate- and strenuous-intensity activity is also advisable along with resistance training for at least two non-successive days per week [87].

Similarly, once GDM is diagnosed, all patients should receive diet and exercise counselling, as it is estimated that 70–85% of cases can be controlled with lifestyle changes only [88]. The goals of nutritional therapy in GDM are to achieve normoglycemia, prevent ketosis, provide adequate weight gain on the basis of maternal BMI and contribute to foetal well-being. There is sparse level I evidence to support specific nutritional prescription for GDM. Caloric requirement is 30 kcal/kg/day for normal weight, 22–25 kcal/kg/day for overweight and 12–14 kcal/kg/day for morbidly obese GDM subjects (present pregnant weight). For underweight women, the caloric requirement may be up to 40 kcal/kg/day. Severe calorie restriction to <1500 kcal/day is not advisable because of increased risk for ketonemia [89]. Calorie intake from carbohydrate should be restricted to 33–40%, with the remaining calories divided between protein (20%) and fat (40%) [90]. Low glycemic index (<55) is recommended as it has been shown that the glycemic index of the food can affect the birth weight of the baby [91]. Maternal weight changes are also important, since women diagnosed with GDM who had gestational weight gain above the Institute of Medicine (IOM) guidelines experienced higher risk of adverse outcomes, such as preterm delivery, having macrosomic infants, and caesarean delivery [92]. The IOM recommendations for gestational weight gain [93] are shown in Table 16.5. Weight loss during pregnancy is not advisable; nevertheless, controversy exists regarding this

Table 16.5 New recommendations of Institute of Medicine for total and rate of weight gain during pregnancy, by pre-pregnancy body mass index (BMI)

Pre-pregnancy BMI	Total weight gain range in kg	Rates of weight gain (2nd and 3rd trimester) mean (range) in kg/week
Underweight (<18.5 kg/m^2)	12.5–18	0.51 (0.44–0.58)
Normal weight (18.5–24.9 kg/m^2)	11.5–16	0.42 (0.35–0.50)
Overweight (25.0–29.9 kg/m^2)	7–11.5	0.28 (0.23–0.33)
Obese ($\geq$ 30.0 kg/m^2)	5–9	0.22 (0.17–0.27)

Legend The Institute of Medicine provides recommendations for gestational weight gain

recommendation for morbidly obese women. Exercise or increased physical activity, has been shown to decrease peripheral insulin resistance and improve glycaemic control, therefore should be part of a lifestyle change in women with GDM. In a recent review, Mottola et al. [94] recommend walking or aerobic activity moving large muscle groups or body weight supported activity such as stationary cycling or swimming in sessions of 25–40 min at least 3 times per week, preferably after a meal.

In conclusion, life-style modification with appropriate nutrition and physical activity plays a pivotal role in the treatment of both PCOS and GDM and is considered to be the base of the therapeutical approach for both entities.

Pharmacological Agents

Insulin-sensitizing agents are a hallmark of the treatment of PCOS, with metformin being the most frequently used medication. At the same time, despite the fact that insulin therapy has been considered the gold standard for the treatment of GDM, recent evidence supports the beneficial effects of metformin in pregnancies complicated by GDM.

Metformin has been shown to ameliorate several parameters in PCOS, including hormonal (LH, androstenedione, dehydroepiandrosterone sulphate (DHEAS), testosterone, free androgen index and fasting insulin), metabolic as BMI and blood pressure as well as clinical parameters as menstrual cyclicity [95]. Improvement of several other indices associated with metabolic dysfunction in PCOS subjects is linked to metformin treatment, such as insulin resistance, endothelial dysfunction, oxidative stress, dyslipidemia [96] atherogenic molecules like C-reactive protein [97], endothelin 1, Intercellular Adhesion Molecule (ICAM), Vascular Cell Adhesion Molecule (VCAM) [98] and AGEs [99]. Metformin exhibits its beneficial effect in both obese and lean women with PCOS and thus in different PCOS phenotypes [100]. The potential of this biguanide has also been evaluated during the pregnancy of women with PCOS. A meta-analysis of 1106 patients found that metformin administration throughout pregnancy decreased the odds ratio of early pregnancy loss, GDM, preeclampsia and preterm delivery in PCOS women with no serious adverse side effects [101]. Another meta-analysis assessing metformin treatment in persons at risk for diabetes mellitus found that metformin reduces new-onset diabetes by 40% [102]. Nevertheless, a randomized, placebo-controlled, double-blind, multicenter study by Vanky et al. [21] showed that metformin treatment throughout gestation did not reduce pregnancy complications in PCOS, as the prevalence of preeclampsia, preterm delivery and gestational diabetes was comparable between the metformin and placebo groups. Metformin may even have a role in infertility treatment of women with PCOS, especially in those with obesity [103]. A multicenter, randomized, double-blind, placebo-controlled study among women with PCOS and anovulatory infertility showed that a 3-month pretreatment with metformin, combined thereafter with an ovulation induction agent, if needed, and continued throughout the first pregnancy trimester improved pregnancy rates and live birth rates [104]. The

above data suggest a potential of metformin in ameliorating the pregnancy outcome of women with PCOS, nevertheless the results of on-going randomized controlled studies should be awaited before definite guidelines recommend metformin use in pregnant women with PCOS. Until then, the treatment of each pregnant woman with PCOS should be individualized.

Regarding the use of metformin in pregnant women with GDM, the first major trial comparing metformin and/or insulin, the MiG-study by Rowan et al. [105], concluded that metformin treatment, compared with insulin, results in similar perinatal outcomes, improves insulin sensitivity in the mother and offspring, is associated with less weight gain during pregnancy and has better treatment acceptability. Nevertheless, in this study, 46% of the patients on metformin required supplemental insulin to meet the glycaemic targets. Several other studies have elucidated the effectiveness of metformin in treating GDM. A randomized controlled study by Niromanesh et al. [106] showed that the offspring's birth weight was lower in the metformin group compared to insulin group, without reaching statistical significance, in comparison to maternal weight gain which was significantly lower in the metformin group. In a recently published randomized placebo-controlled trial which included obese pregnant women without diabetes mellitus, metformin treatment was associated with less maternal gestational weight gain and a lower incidence of preeclampsia compared to placebo. The incidence of gestational diabetes, LGA neonates, or adverse neonatal outcomes was comparable between the groups in the same study [107]. In conclusion, metformin appears to be effective for the treatment of GDM, especially for overweight or obese women, and has a good safety profile. However, a significant number of patients may not meet the glycaemic goals with metformin only and may require insulin supplementation. Evidence suggests that there are possible advantages for the use of metformin over insulin in GDM regarding maternal weight gain and neonatal outcomes.

The administration and the effects of inositol phosphoglycan (mainly its stereoisomers D-chiro-inositol and myo-inositol), one of the intracellular mediators of insulin signalling, has been assessed both in PCOS and GDM. Both inositols have been shown to be effective in ameliorating PCOS metabolic aspects such as insulin resistance, dyslipidemia and abnormal glucose metabolism. Reproductive morbidities affecting PCOS women, such as hyperandrogenemia, irregular menstrual cycle and anovulation seem to be improved mostly by myo-inositol [108]. Myo-inositol may even have a role in reducing the development of GDM, as proposed both by a meta-analysis [109] and by a recently published RCT on overweight women [110].

To summarize, metformin is the only pharmacological agent to target pathophysiological mechanisms of both PCOS and GDM, giving this biguanide a fundamental role among the current treatment strategies for both entities.

Conclusions

PCOS and GDM are prevalent disorders through the female cycle life. They share common pathophysiological mechanisms with insulin resistance being the most predominant. While GDM is the most frequently described pregnancy complication in PCOS, several other gestational morbidities are met in both disorders, therefore pregnancies of PCOS subjects or those complicated by GDM should be considered as high risk and intensified surveillance is recommended. Moreover, physicians treating women with PCOS and GDM should always take into consideration the high risk of these women to develop metabolic syndrome and type 2 diabetes. Appropriate therapeutic approach, always including life-style modification, is warranted to ameliorate symptoms, target pathogenetic mechanisms and possibly prevent the development of long-term consequences of the two entities. Metformin can be a useful and effective treatment modality for both PCOS and GDM.

References

1. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030.
2. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
3. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The androgen excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
4. Zawadski J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens J, Haseltine F, Merriam G, editors. Polycystic ovary syndrome. Boston, MA: Blackwell Scientific Publications, 1992. p. 37784.
5. Livadas S, Diamanti-Kandarakis E. Polycystic ovary syndrome: definitions, phenotypes and diagnostic approach. Front Hormon Res. 2013;40:1–21.
6. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000;85(7):2434–8.
7. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004;89(6):2745–9.
8. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab. 1999;84(11):4006–11.
9. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev. 2015;36(5):487–525.
10. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus, vol. 30(Suppl 2); 2007. p. S251–60.
11. Yogev Y, Metzger BE, Hod M. Establishing diagnosis of gestational diabetes mellitus: impact of the hyperglycemia and adverse pregnancy outcome study. Semin Fetal Neonatal Med. 2009;14(2):94–100.
12. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676–82.
13. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014;103(3):341–63.
14. Standards of medical care in diabetes—2014. Diabetes Care. 2014;37 Suppl 1:S14–80.
15. Poomalar GK. Changing trends in management of gestational diabetes mellitus. World J Diabetes. 2015;6 (2):284–95.
16. Jiwani A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG. Gestational diabetes mellitus: results from a survey of country prevalence and practices. J Matern-fetal Neonatal Med. 2012;25(6):600–10 (The Official Journal of the European Association of Perinatal Medicine, The Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet).
17. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PLoS ONE. 2014;9(6):e97871.
18. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: a clinical update. World J Diabetes. 2015;6(8):1065–72.
19. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.
20. Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, Chen HY. Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biol Endocrinol (RB&E). 2013;11:56.
21. Vanky E, Stridsklev S, Heimstad R, Romundstad P, Skogoy K, Kleggetveit O, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. J Clin Endocrinol Metab. 2010;95(12):E448–55.
22. Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. BMJ. 2011;343:d6309 (Clinical research ed).
23. Palomba S, Falbo A, Chiossi G, Muscogiuri G, Fornaciari E, Orio F, et al. Lipid profile in nonobese pregnant women with polycystic ovary syndrome: a prospective controlled clinical study. Steroids. 2014;88:36–43.

24. de Wilde MA, Veltman-Verhulst SM, Goverde AJ, Lambalk CB, Laven JS, Franx A, et al. Preconception predictors of gestational diabetes: a multicentre prospective cohort study on the predominant complication of pregnancy in polycystic ovary syndrome. Hum Reprod. 2014;29(6):1327–36 (Oxford, England).
25. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21(5):575–92.
26. Kousta E, Cela E, Lawrence N, Penny A, Millauer B, White D, et al. The prevalence of polycystic ovaries in women with a history of gestational diabetes. Clin Endocrinol. 2000;53(4):501–7.
27. Holte J, Gennarelli G, Wide L, Lithell H, Berne C. High prevalence of polycystic ovaries and associated clinical, endocrine, and metabolic features in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab. 1998;83(4):1143–50.
28. Palomba S, La Sala GB. Pregnancy complications in women with polycystic ovary syndrome: importance of diagnostic criteria or of phenotypic features? Hum Reprod. 2015 (Oxford, England).
29. Rojas J, Chavez-Castillo M, Bermudez V. The role of metformin in metabolic disturbances during pregnancy: polycystic ovary syndrome and gestational diabetes mellitus. Int J Reprod Med. 2014;2014:797681.
30. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care. 2008;31(Suppl 2):S262–8.
31. Sekar N, Garmey JC, Veldhuis JD. Mechanisms underlying the steroidogenic synergy of insulin and luteinizing hormone in porcine granulosa cells: joint amplification of pivotal sterol-regulatory genes encoding the low-density lipoprotein (LDL) receptor, steroidogenic acute regulatory (stAR) protein and cytochrome P450 side-chain cleavage (P450scc) enzyme. Mol Cell Endocrinol. 2000;159(1–2):25–35.
32. Diamanti-Kandarakis E. Polycystic ovarian syndrome: pathophysiology, molecular aspects and clinical implications. Expert Rev Mol Med. 2008;10:e3.
33. Diamanti-Kandarakis E, Argyrakopoulou G, Economou F, Kandaraki E, Koutsilieris M. Defects in insulin signaling pathways in ovarian steroidogenesis and other tissues in polycystic ovary syndrome (PCOS). J Steroid Biochem Mol Biol. 2008;109(3–5):242–6.
34. Hill JW, Elmquist JK, Elias CF. Hypothalamic pathways linking energy balance and reproduction. Am J Physiol Endocrinol Metab. 2008;294(5):E827–32.
35. Eyvazzadeh AD, Pennington KP, Pop-Busui R, Sowers M, Zubieta JK, Smith YR. The role of the endogenous opioid system in polycystic ovary syndrome. Fertil Steril. 2009;92(1):1–12.
36. Baillargeon JP, Nestler JE. Commentary: polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab. 2006;91(1):22–4.
37. Selva DM, Hogeveen KN, Innis SM, Hammond GL. Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene. J Clin Invest. 2007;117(12):3979–87.
38. Du X, Rosenfield RL, Qin K. KLF15 is a transcriptional regulator of the human 17beta-hydroxysteroid dehydrogenase type 5 gene. A potential link between regulation of testosterone production and fat stores in women. J Clin Endocrinol Metab. 2009;94(7):2594–601.
39. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;27(10):3067–73 (Oxford, England).
40. Diamanti-Kandarakis E, Panidis D. Unravelling the phenotypic map of polycystic ovary syndrome (PCOS): a prospective study of 634 women with PCOS. Clin Endocrinol. 2007;67(5):735–42.
41. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Alvero R, et al. The pregnancy in polycystic ovary syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial. Fertil Steril. 2014;101(1):258-69.e8.
42. Livadas S, Kollias A, Panidis D, Diamanti-Kandarakis E. Diverse impacts of aging on insulin resistance in lean and obese women with polycystic ovary syndrome: evidence from 1345 women with the syndrome. Eur J Endocrinol/Eur Fed Endocr Soc. 2014;171(3):301–9.
43. Diamanti-Kandarakis E, Katsikis I, Piperi C, Kandaraki E, Piouka A, Papavassiliou AG, et al. Increased serum advanced glycation end-products is a distinct finding in lean women with polycystic ovary syndrome (PCOS). Clin Endocrinol. 2008;69(4):634–41.
44. Witchel SF, Recabarren SE, Gonzalez F, Diamanti-Kandarakis E, Cheang KI, Duleba AJ, et al. Emerging concepts about prenatal genesis, aberrant metabolism and treatment paradigms in polycystic ovary syndrome. Endocrine. 2012;42(3):526–34.
45. Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. J Clin Endocrinol Metab. 2011;96(3):E480–4.
46. Chevalier N, Fenichel P. Bisphenol A. Targeting metabolic tissues. Rev Endocr Metab Disord. 2016.
47. Rosenfield RL. Clinical review: identifying children at risk for polycystic ovary syndrome. J Clin Endocrinol Metab. 2007;92(3):787–96.
48. Ibanez L, Dimartino-Nardi J, Potau N, Saenger P. Premature adrenarche—normal variant or forerunner of adult disease? Endocr Rev. 2000;21(6):671–96.

49. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(Suppl 2):S112–9.
50. Tzanavari T, Giannogonas P, Karalis KP. TNF-alpha and obesity. Curr Dir Autoimmun. 2010;11:145–56.
51. Kawano J, Arora R. The role of adiponectin in obesity, diabetes, and cardiovascular disease. J Cardiometab Syndr. 2009;4(1):44–9.
52. Chen J, Tan B, Karteris E, Zervou S, Digby J, Hillhouse EW, et al. Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. Diabetologia. 2006;49(6):1292–302.
53. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod. 2002;17(11):2858–64 (Oxford, England).
54. Palomba S, Falbo A, Chiossi G, Orio F, Tolino A, Colao A, et al. Low-grade chronic inflammation in pregnant women with polycystic ovary syndrome: a prospective controlled clinical study. J Clin Endocrinol Metab. 2014;99(8):2942–51.
55. Yogev C, Hod C, Oats MI, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) study: preeclampsia. Am J Obstet Gynecol. 2010;202(3):255.e1-7.
56. Dudley DJ. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. Obstet Gynecol Clin North Am. 2007;34(2):293–307, ix.
57. Hillier TA, Pedula KL, Vesco KK, Schmidt MM, Mullen JA, LeBlanc ES, et al. Excess gestational weight gain: modifying fetal macrosomia risk associated with maternal glucose. Obstet Gynecol. 2008;112(5):1007–14.
58. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. Int J Gynaecol Obstet Official Organ Int Fed Gynaecol Obstet. 2004;87(3):220–6.
59. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril. 2005;83(5):1454–60.
60. Cerda C, Perez-Ayuso RM, Riquelme A, Soza A, Villaseca P, Sir-Petermann T, et al. Nonalcoholic fatty liver disease in women with polycystic ovary syndrome. J Hepatol. 2007;47(3):412–7.
61. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91(1):48–53.
62. Ehrmann DA, Kasza K, Azziz R, Legro RS, Ghazzi MN. Effects of race and family history of type 2 diabetes on metabolic status of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(1):66–71.
63. Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab. 2005;90(6):3236–42.
64. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2011;95(3):1073–9.e1-11.
65. Wild RA. Polycystic ovary syndrome: a risk for coronary artery disease? Am J Obstet Gynecol. 2002;186(1):35–43.
66. Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. J Clin Endocrinol Metab. 2001;86(10):4666–73.
67. Carmina E, Orio F, Palomba S, Longo RA, Cascella T, Colao A, et al. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. Am J Med. 2006;119(4):356.e1-6.
68. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet (London, England). 2009;373(9677):1773–9.
69. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25(10):1862–8.
70. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. Can Med Assoc J (CMAJ) journal de l'Association medicale canadienne. 2008;179(3):229–34.
71. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. J Clin Endocrinol Metab. 2010;95(2):670–7.
72. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008;31(8):1668–9.
73. Boutzios G, Livadas S, Piperi C, Vitoratos N, Adamopoulos C, Hassiakos D, et al. Polycystic ovary syndrome offspring display increased oxidative stress markers comparable to gestational diabetes offspring. Fertil Steril. 2013;99(3):943–50.
74. Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab. 2008;93(5):1662–9.
75. Carlsen SM, Jacobsen G, Vanky E. Mid-pregnancy androgen levels are negatively associated with breastfeeding. Acta Obstet Gynecol Scand. 2010;89(1):87–94.
76. Sir-Petermann T, Codner E, Perez V, Echiburu B, Maliqueo M, Ladron de Guevara A, et al. Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94(6):1923–30.

77. Kosidou K, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, et al. Maternal polycystic ovary syndrome and the risk of autism spectrum disorders in the offspring: a population-based nationwide study in Sweden. Mol Psychiatry. 2015.
78. Vaarasmaki M, Pouta A, Elliot P, Tapanainen P, Sovio U, Ruokonen A, et al. Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. Am J Epidemiol. 2009;169(10):1209–15.
79. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. Diabetes. 1988;37(5):622–8.
80. Lyall K, Pauls DL, Spiegelman D, Ascherio A, Santangelo SL. Pregnancy complications and obstetric suboptimality in association with autism spectrum disorders in children of the Nurses' Health Study II. Autism Res Official J Int Soc Autism Res. 2012;5(1):21–30.
81. Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. Association of maternal diabetes with autism in offspring. JAMA. 2015;313(14):1425–34.
82. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Women's Health. 2011;3:25–35.
83. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88(2):812–9.
84. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2011;17(2):171–83.
85. Ujvari D, Hulchiy M, Calaby A, Nybacka A, Bystrom B, Hirschberg AL. Lifestyle intervention up-regulates gene and protein levels of molecules involved in insulin signaling in the endometrium of overweight/obese women with polycystic ovary syndrome. Hum Reprod. 2014;29(7):1526–35 (Oxford, England).
86. Hulchiy M, Nybacka A, Sahlin L, Hirschberg AL. Endometrial expression of estrogen receptors and the androgen receptor in women with polycystic ovary syndrome—a lifestyle intervention study. J Clin Endocrinol Metab. 2015:jc20153803.
87. Panidis D, Tziomalos K, Papadakis E, Vosnakis C, Chatzis P, Katsikis I. Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome: impact on metabolism and fertility. Endocrine. 2013;44(3):583–90.
88. American Diabetes Association. Management of diabetes in pregnancy. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38 Suppl. 1:S77–S79.
89. Rizzo T, Metzger BE, Burns WJ, Burns K. Correlations between antepartum maternal metabolism and child intelligence. N Engl J Med. 1991;325(13):911–6.
90. Practice Bulletin No. 137: Gestational diabetes mellitus. Obstet Gynecol. 2013;122(2 Pt 1):406–16.
91. Moses RG, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, et al. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 2006;84(4):807–12.
92. Cheng YW, Chung JH, Kurbisch-Block I, Inturrisi M, Shafer S, Caughey AB. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. Obstet Gynecol. 2008;112(5):1015–22.
93. Institute of Medicine and National Research Council Committee to Reexamine IOMPWG. The National Academies Collection: Reports funded by National Institutes of Health. In: Rasmussen KM, Yaktine AL, editors. Weight gain during pregnancy: reexamining the guidelines. Washington (DC): National Academies Press (US) National Academy of Sciences; 2009.
94. Mottola MF, Artal R. Fetal and maternal metabolic responses to exercise during pregnancy. Early Hum Dev. 2016.
95. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol/Eur Fed Endocr Soc. 2010;162(2):193–212.
96. Kocer D, Bayram F, Diri H. The effects of metformin on endothelial dysfunction, lipid metabolism and oxidative stress in women with polycystic ovary syndrome. Gynecol Endocrinol Official J Int Soc Gynecol Endocrinol. 2014;30(5):367–71.
97. Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanainen JS. Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88 (10):4649–54.
98. Diamanti-Kandarakis E, Alexandraki K, Protogerou A, Piperi C, Papamichael C, Aessopos A, et al. Metformin administration improves endothelial function in women with polycystic ovary syndrome. Eur J endocrinol/Eur Fed Endocr Soc. 2005;152(5):749–56.
99. Diamanti-Kandarakis E, Alexandraki K, Piperi C, Aessopos A, Paterakis T, Katsikis I, et al. Effect of metformin administration on plasma advanced glycation end product levels in women with polycystic ovary syndrome. Metab Clin Exp. 2007;56(1):129–34.
100. Tan S, Hahn S, Benson S, Dietz T, Lahner H, Moeller LC, et al. Metformin improves polycystic ovary syndrome symptoms irrespective of pre-treatment insulin resistance. Eur J Endocrinol/Eur Fed Endocr Soc. 2007;157 (5):669–76.

101. Zheng J, Shan PF, Gu W. The efficacy of metformin in pregnant women with polycystic ovary syndrome: a meta-analysis of clinical trials. J Endocrinol Invest. 2013;36(10):797–802.
102. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med. 2008;121(2):149-57.e2.
103. Diamanti-Kandarakis E. Reproductive endocrinology: infertility treatment in PCOS–is metformin in from the cold? Nat Rev Endocrinol. 2012;8(6):328–30.
104. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippelainen M, Perheentupa A, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab. 2012;97(5):1492–500.
105. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358(19):2003–15.
106. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract. 2012;98 (3):422–9.
107. Syngelaki A, Nicolaides KH, Balani J, Hyer S, Akolekar R, Kotecha R, et al. Metformin versus placebo in obese pregnant women without diabetes mellitus. N Engl J Med. 2016;374(5):434–43.
108. Facchinetti F, Bizzarri M, Benvenga S, D'Anna R, Lanzone A, Soulage C, et al. Results from the international consensus conference on Myo-inositol and d-chiro-inositol in obstetrics and gynecology: the link between metabolic syndrome and PCOS. European Journal of Obstetrics, Gynecology, and Reproductive Biology, vol. 195, 2015. p. 72–6.
109. Zheng X, Liu Z, Zhang Y, Lin Y, Song J, Zheng L, et al. Relationship between myo-inositol supplementary and gestational diabetes mellitus: a meta-analysis. Medicine. 2015;94(42):e1604.
110. Santamaria A, Di Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, et al. Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. J Matern-Fetal Neonatal Med. 2015:1–4 (The Official Journal of the European Association of Perinatal Medicine, The Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetrics).

Chapter 17
Bariatric Surgery and Its Impact on Gestational Diabetes

Gil Gutvirtz, Charlotte Alexander and Eyal Sheiner

Key Points

- Obesity is a growing epidemic.
- One in five women is obese at time of conception.
- Obesity is associated with high risk for pregnancy complications such as GDM, preeclampsia, and large neonates.
- BS significantly reduces the risk for obesity and its associated complications, i.e., GDM, preeclampsia, and large neonates.
- Women who become pregnant after bariatric surgery may have an increased risk for small for gestational age infants.
- Although rare, post-surgical complications might be life-threatening and high index of suspicion should be considered especially after RYGB procedure.
- Pregnancy after BS is not associated with adverse perinatal outcomes.

Keywords Obesity · Gestational diabetes mellitus · Bariatric surgery · Pregnancy complications · Perinatal outcomes

Abbreviations

BMI	Body mass index
DM	Diabetes mellitus
GDM	Gestational diabetes mellitus
BS	Bariatric surgery
CD	Cesarean delivery

G. Gutvirtz (✉) · C. Alexander · E. Sheiner
Department of Obstetrics and Gynecology, "Soroka" University Medical Center,
Ben-Gurion University of the Negev, Rager Boulevard, P.O.B 151, 85025 Be'er Sheva, Israel
e-mail: Giltzik@gmail.com

C. Alexander
e-mail: clcalexander@gmail.com

E. Sheiner
e-mail: Sheiner@bgu.ac.il

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_17

Introduction

Overweight and obesity, defined as body mass index [BMI] >25 and BMI over 30 kg/m^2, respectively, is becoming more common worldwide. According to the latest WHO fact sheet on obesity, in 2014, more than 1.9 billion adults 18 years and older, were overweight (BMI > 25). Of these, over 600 million were obese, making 39% of the world's adult population overweight, out of which 13% (11% of men and 15% of women) are considered obese [1].

In 2011–2012 in the United States, 36% of adult women were obese [2], and the majority of women in early pregnancy were either overweight or obese (BMI > 25) [3]. It is estimated that 1 out of 3 pregnant women is considered either overweight or obese [4, 5]. These findings can eventually lead to adverse consequences for their pregnancies and long-term health.

Maternal obesity in pregnancy is a well-established risk factor for numerous maternal and perinatal complications, including gestational diabetes mellitus (GDM), gestational hypertension, and higher rates of cesarean deliveries [6–9]. Studies have shown that the risk for complications increases as pre-pregnancy BMI rises [10–12]. Consequently, GDM is becoming more prevalent with its negative pregnancy outcomes such as large for gestational age (LGA) fetuses and macrosomia, preeclampsia and stillbirth also on the rise [13–16].

The mother affected by GDM is at an increased risk for developing type 2 diabetes mellitus (T2DM) later in life, and is also susceptible to future cardiovascular and renal complications compared to non-overweight non-GDM women [17–19]. Other Long-term maternal complications include higher risk for ophthalmic disease [20], and even gynecological malignancies such as ovarian and breast cancer [21].

Short-term complications are also expected for the infant of the diabetic mother and include hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia, respiratory distress, and/or cardiomyopathy [22, 23]. Most of these complications are transient and dependent on maternal control of hyperglycemia. However, long-term sequelae are also concerning with increased risks for the offspring to develop obesity, impaired glucose tolerance, or metabolic syndrome [24–27].

It is strongly advised to encourage obese women to reduce weight pre-conception. While weight reduction programs show modest results in obese and morbidly obese patients, surgical treatment has a great potential to treat obese women in reproductive age [28]. More than 70% of bariatric operations are performed in women [29] with the majority in women of reproductive age. Large studies show promising results in achieving sustainable weight reduction, prevention and even resolution of diabetes.

Bariatric Surgery Versus Conventional Medical Therapy

As the proportion of obesity increases in global populations, different methods have been compared to find the most effective way to lose weight. Schauer et al. [30] tested weight loss and T2DM results in patients after bariatric surgery (BS) with intensive medical therapy to patients after intensive medical therapy only. Bariatric surgeries included both Roux-en-Y procedures and sleeve gastrectomies (discussed later in this chapter). Intensive medical therapy included lifestyle counseling, diabetes counseling, weight management, frequent home glucose monitoring and drug therapies like incretin analogs. Twelve months after therapy, patients receiving BS lost 20–25 kgs more than their counterparts receiving only intensive medical therapy. The surgical patients also achieved better glycemic control with HbA1C levels 1% lower than the control. In a 3-year follow-up [31], bariatric patients and their controls had maintained a similar level of weight loss but bariatric patients had achieved better HbA1C levels. Mingrone et al. [32] found similar results, with patients after bariatric surgeries

also achieving 75–95% (depending on surgery methods) remission of T2DM and controls having no remission of T2DM. These studies have shown BS is more effective than conventional therapy in both weight loss and remission of T2DM.

Bariatric Surgical Methods

BS is an increasingly popular method of weight loss for very overweight patients [33]. It is indicated for patients with BMI > 40 or BMI > 35 with associated medical comorbidities (metabolic disorders, cardiorespiratory disease, severe joint disease, etc.) who have failed to lose weight by conservative means like diet, exercise, and weight loss medications. This also includes patients who have previously lost weight with conservative methods but have regained it [34]. Patients with BS have achieved remarkable weight loss, with patients losing upwards of 60% excess weight at 2-year follow-up [35].

BS is a term referring to many different surgical methods and procedures. It is usually categorized as three methods: restrictive (decreasing the patient's food intake), mal-absorptive (limiting the patient's ability to absorb the usual amount of food they eat) or a combination of the two. Restrictive methods include gastric banding and sleeve gastrectomy as well as more archaic surgeries like jaw wiring. Mal-absorptive surgeries shorten the length of the intestines, thus decreasing the surface area available to absorb calories from food.

Adjustable Gastric Banding

Adjustable gastric banding is often performed laparoscopically and is thus referred to as LAGB (Laparoscopic Adjustable Gastric Banding). This method places an inflatable band around the proximal stomach and fundus. The band is attached to a port accessible subcutaneously to allow for adjustment of the band [36] (Fig. 17.1). Tightening or inflating the band leads to restriction of the stomach, reduced filling capacity, and early satiety. Patients continue to follow-up and have their gastric band adjusted based on weight loss and hunger levels. Five years after surgery, patients have lost an average of 60% excess weight [37].

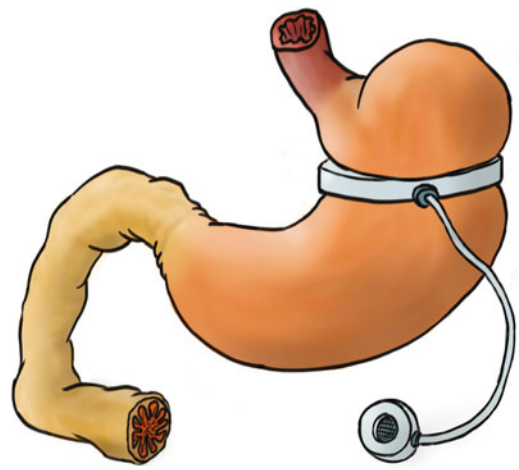


Fig. 17.1 Gastric banding. Acknowledgements to Dr. Gluhoded for his artwork

Sleeve Gastrectomy

Sleeve gastrectomy is a gastric resection, and like gastric banding, is also usually performed laparoscopically [38]. The greater curvature of the stomach is devascularized and then removed, leaving a sleeve of stomach that is only about as wide as the duodenum (Fig. 17.2). The reduced volume of stomach results in early satiety. Patients have been shown to lose 55% of excess weight after 5 years [39]. This procedure is preferred in high-risk morbidly obese patients and other patients with higher surgical risks because it can be performed in less than 80 min.

Roux-En-Y Gastric Bypass

Roux-en-Y Gastric Bypass [RYGB] is a more radical surgery than involves the creation of a small proximal gastric pouch totally separated from the rest of the stomach. Proximal jejunum (Roux Limb) is then anastomosed to this pouch and the distal enterostomy is anastomosed 75–150 cm along the Roux Limb (Fig. 17.3). The small gastric pouch acts as intake restriction and should not include the fundus because the fundus can dilate over time. A longer length of the Roux limb, and thus the longer the bypass, increases rates of initial weight loss. RYGB patients have been shown to lose between 60 and 80% of their excess body weight in the first year after surgery [40]. RYGB is reserved for superobese patients and patients who have failed in restrictive diets. Because RYGB relies on malabsorption for weight loss, these patients must also take vitamin and mineral supplements and be followed more closely postoperatively than patients with restrictive operations.

Although these procedures are helpful in assisting patients to lose weight in the short term, some studies show long-term failure to maintain weight loss or even regain of lost weight. A 5, 7 and 10 year follow-up of LABG and RYGB patients showed a 50% failure rate in LABG and successful weight loss in Roux-en-Y, despite 9 life-threatening and 1 death due to Roux-en-Y complications [41]. A 5-year follow-up on Roux-en-Y patients showed no significant decrease in BMI 24 months after surgery with weight regain by 48 months after surgery [42]. A 10 year follow-up on Roux-en-Y patients showed 20.4–34.9% failure rates [43].

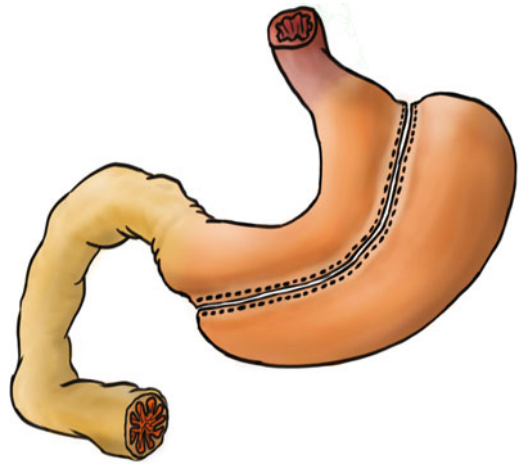


Fig. 17.2 Sleeve gastrectomy. Acknowledgements to Dr. Gluhoded for his artwork

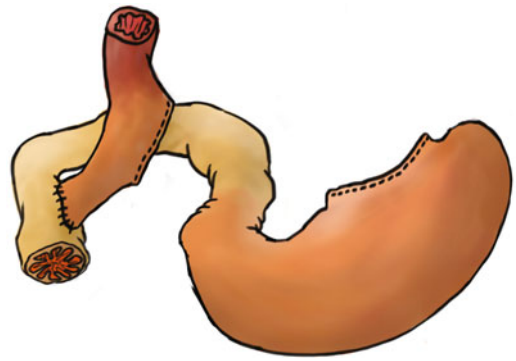


Fig. 17.3 Gastric bypass. Acknowledgements to Dr. Gluhoded for his artwork

Post-bariatric Pregnancy

In general, BS lowers the risk for obesity-related pregnancy complications such as GDM and gestational hypertension, and also provides favorable pregnancy outcomes including lower rates of CS and LGA babies. A retrospective study by Sheiner et al. [44] comparing pregnancy outcomes of different types of BS concluded that all procedures have basically comparable perinatal outcomes. It is important to clarify that the mentioned favorable outcomes are probably not related to the surgery itself but due to the weight loss and lower BMI that post-BS women achieve at the beginning of their pregnancy.

Bariatric Surgery and GDM

Obesity and pre-pregnancy weight gain are major risk factors for GDM [45, 46]. Reducing weight prior to conception is probably the most effective mean to lower obesity-related complications of pregnancy. Overall, most observational studies on post-bariatric pregnancies found BS to lower rates of GDM as they compare post-surgery women with obese controls. Main studies are summarized in Table 17.1.

Studies that compared post-bariatric pregnancies with the general population found conflicting data. Belogolovkin et al. [47] showed lower risk for GDM [OR 0.44, CI 0.26–0.76] in pregnancies following BS compared to a large population cohort of pregnancies without BS, while other studies found higher prevalence of GDM among postoperative women in comparison to the general population [48–50]. Sheiner et al. [51] found an increased risk for GDM in the BS group compared to the general population (9.4 vs. 5%). The authors explained that higher rates were found since the postoperative women were still more likely to be obese as compared with the general population. No significantly increased risk was found after confounders such as maternal BMI were controlled for. Other studies also did not reach statistical significant [52, 53]. Although no clear conclusion can be made based on these studies, Burke et al. [54] did demonstrate that BS could reduce the risk of GDM from the rate in similar obese parturient to a rate equivalent with the general population (27 vs. 8%, OR 0.23, CI 0.15–0.36) and a recent large Swedish study confirmed this reduction in GDM having matched up to five control pregnancies to each pregnancy after BS [55]. Johansson and colleagues showed in this study that only 1.9% of post-BS women had GDM compared to 6.8% of matched controls ($p < 0.001$).

While the comparison between incidence of GDM in post-bariatric women and the general population needs further investigation, when comparing these women to a more relevant, obese

Table 17.1 Selected studies on gestational diabetes mellitus (GDM) in pregnancy before and after bariatric surgery (BS)

Study	Cases (pregnancies)	Controls (pregnancies)	Type of BS	Cases (%)	Controls (%)	OR	95% CI	Comments
Sheiner et al. [51] 2004, Israel	298	158,912	BS	9.4	5.0			Compared to general obstetric population NS when controlled for BMI
Bologolovkin et al. [47] 2012, USA	293	656,353	BS	NR	NR	0.44	0.26–0.76	Compared to general obstetric population
Josefsson et al. [53], 2011 Sweden	126	188,500	BS	0.8	0.5	NS	NS	Compared to general obstetric population
Burke et al. [54], 2010 USA	354	346	BS	8	27	0.23	0.15–0.36	
Lapolla et al. [57] 2010, Italy	83	120 BMI $\geq$ 40	LAGB	6.0	50.0	0.47	0.38–0.58	The comparison group of 858 normal weight women were all without GDM so no comparison was made
		858 normal BMI			–	–	–	
	27	27 pre-surgery - same women		7.4	7.4	NS	NS	
Sheiner et al. [78] 2011, Israel	104 < 1st post-op year	358 > 1st post-op year	BS	10.5	7.3	NS	NS	Women who conceived during or after the first postoperative year
Aricha-Tamir et al. [63] 2011, Israel	144	144	BS	5.7	19.3	0.2	0.1-0.5	Pregnancies before and after BS in the same women
Amsalem et al. [64] 2013, Israel	109	109	Restrictive (LAGB, SRVG)	5.6	19.0	0.2	0.06–0.48	Reduced risk significant also for second pregnancy following BS
Berlac et al. [75] 2014, Denmark	415	827 obese	RYGB	9.2	8.1	RR = 6.0		RR was calculated comparing to the normal weight controls (reference group)
		829 normal weight			1.3	RR = 6.9		
Shai et al. [59] 2014, Israel	326	1612	BS	10.1	14.7	0.6	0.44–0.9	
Johansson et al. [55] 2015, Sweden	597	2356	BS	1.9	6.8	0.25	0.13–0.47	
Adams et al. [61] 2015, USA	295	295	RYGB	3.4	8.8	0.33	0.13–0.77	

BS Bariatric surgery; *LAGB* Laparoscopic adjustable gastric banding; *SRVG* Silastic ring vertical gastroplasty; *RYGB* Roux-en-Y gastric bypass; *NS* No significant difference; *RR* Relative risk; *NR* Not reported; *BMI* Body mass index

counterpart, results are encouraging. A majority of studies comparing post-bariatric pregnancies to pre-bariatric or no BS obese parturients, show a significant reduction in GDM rates [47, 54, 56–61]. Shai et al. [59] found BS to be an independent protective factor for GDM in the BS group compared to obese women (OR 0.6, CI 0.4–0.9, $P < 0.05$). Weintraub et al. [62] also found BS to be independently associated with a reduction in diabetes mellitus (OR 0.42, CI 0.26–0.67, $P < 0.001$) when comparing pregnancies of obese women before and after BS.

Another significant study compared pregnancies of the same women before and after BS. Aricha-Tamir et al. [63] studied 144 pregnancies of women before BS and compared them to 144 pregnancies of the same women following BS. They showed a prominent decrease in GDM after BS that remained significant after subtracting pre-gestational diabetes (19.3 vs. 5.7%, OR 0.2, CI 0.1–0.5, $P = 0.001$). These findings are further highlighted considering that maternal age was significantly older in the post-BS group which constitutes a major risk factor for the development of GDM. Amsalem et al. [64] showed that the reduction in GDM in the same woman is maintained even at the second subsequent pregnancy following BS. Other studies comparing pregnancies before and after BS in the same women show either similar results [50, 65] or no significance difference [52, 57].

It is important to mention a recent meta-analysis which revealed that when comparison groups were matched for pre-pregnancy BMI, the reduction in GDM mostly disappears, suggesting the obvious link between pre-pregnancy BMI and the development of GDM, and not specifically with postoperative status. This important meta-analysis by Galazis et al. [66] summarizes the results between the different comparison groups. They reviewed 17 non-randomized cohort or case-control studies with high methodological quality scores and concluded that when comparing post-bariatric pregnancies to pregnancies of obese women without surgery, the risk of GDM significantly decreases (OR 0.34, CI 0.18–0.67) $P < 0.001$) and this reduction is maintained when pre-surgery BMI was matched. When comparing post-bariatric pregnancies with prior pregnancies of the same women before BS, or matching for pre-pregnancy BMI, the odds ratio is still protective (OR 0.71 and OR 0.77 respectively) but becomes statistically insignificant. Nevertheless, the overall result of their meta-analysis comparing 2724 post-bariatric pregnancies with 136,075 controls, the relative risk reduction of GDM was roughly half (RR = 0.52, CI 0.45–0.59) with an overall odds ratio of 0.47 (CI 0.40–0.56). This is in accordance with other systematic reviews and meta-analysis that concluded that the incidence of GDM was reduced in women after BS compared to obese women [67–74].

Most studies on the effects of BS on pregnancy and GDM do not distinguish between the kinds of BS. They either study one type of BS or combine together the results from restrictive and mal-absorptive procedures, of which LAGB and Roux-en-Y are the most common. A recent nationwide cohort by Berlac et al. [75] found that women who had undergone gastric bypass were 6.9 times more likely than normal weight controls to develop GDM. However, a subgroup analysis [66] of women who had undergone LAGB found a significant reduction in the odds of developing GDM (OR 0.16, CI 0.09–0.32, $P < 0.001$). The same analysis found that LAGB had a protective effect against other obesity-related complications such as preeclampsia and macrosomia, without raising the risk for small neonates, suggesting a possible advantage to some types of BS over others. The latest published review on BS and the pregnancy complicated by GDM by Willis et al. [72] concluded that whether or not potential differences exist between procedure types, overall, strong evidence exist that BS reduces the risk for GDM.

Sheiner et al. [76] investigated a group of women who underwent BS and developed GDM in following pregnancy and compared their pregnancy outcomes to controls with GDM. Encouragingly, they found no significant differences in obstetric characteristics or pregnancy outcomes and concluded that previous BS in patients with GDM is not associated with adverse perinatal outcomes.

Some authorities [77] recommend delaying pregnancy by at least 12 postoperative months to avoid gestation during the rapid weight loss stage, although this recommendation remains based on largely theoretical risks. Our group [78] compared outcomes in pregnant post-bariatric patients who conceived within the first 12 months after surgery and after 12 months of surgery. Comparable rates of

GDM were documented between the groups. In this study, both groups had similar changes in BMI before getting pregnant, suggesting once again that GDM outcomes are probably related to pre-pregnancy BMI and independent of when women conceive after BS. However, it is not yet known whether pregnancy during this time could lead to a malnourished fetus, due to some protein malnutrition, possibly resulting in complications such as low birthweight or malformation. Adhering to the current recommendation to delay conception for at least 1 year seems reasonable as this kind of view could also suggest that women in the first 12 months of surgery might not yet have the effects of bariatric weight loss that would be seen after the first year following surgery.

Screening for Gestational Diabetes Mellitus

Women post-mal-absorptive BS are more likely to have adverse responses to glucose challenge test (GCT), with 14.8% experiencing hypoglycemia and 64.8% experiencing negative side effects [79]. GCT are not well tolerated especially in those patients who have undergone a procedure with mal-absorptive component such as RYGB, due to the "dumping syndrome" that occurs in approximately 50% of these patients [80]. The ingestion of high amounts of refined sugars leads to a hyperosmolar environment and fluid shift to the small bowel lumen causing distension, cramping, nausea, vomiting, and diarrhea. Restrictive-type bariatric procedures such as LAGB are not reported to cause dumping syndrome. Therefore, women after LAGB procedure can undergo standard testing for GDM. It is suggested that oral glucose tolerance test (OGTT) might not be appropriate for women post-mal-absorptive BS. Reasonable alternatives for screening in these women are measuring glycated hemoglobin (A1C), measuring fasting, and postprandial blood sugars for 1–2 weeks in the second trimester [77, 81]. Although it is not currently the standard, some suggest using continuous glucose monitoring to detect GDM in post-mal-absorptive bariatric parturient [82].

When addressing the issue of BS prior to pregnancy it is also important to mention its impact on other pregnancy complications and outcomes other than its effect on GDM, and mostly hypertensive disorders and fetal growth (i.e., macrosomia).

Gestational Hypertension

Gestational hypertension occurs in about 5–10% of pregnancies. Obese women are 50% more likely to develop hypertension, [83] and an elevated BMI has been shown to be a significant risk factor for developing gestational hypertension by multiple retrospective and prospective studies [6, 47, 84, 85]. Other studies have shown that maternal weight and BMI are independent risk factors for hypertensive disorders including preeclampsia [6, 60, 86, 87]

As BS leads to reduced pre-pregnancy maternal weight and BMI, post-BS women also have lower rates of gestational hypertension and preeclampsia in following pregnancies. Most recent studies examining this outcome show lower rates of hypertensive disorders of pregnancy as summarized in Table 17.2. A recent meta-analysis quantified the effect of BS as reducing rates of preeclampsia by about half [66].

Studies mentioned earlier in this chapter that examined this spectrum of outcomes have generally demonstrated risks to be lower in postoperative women [52, 62, 76, 88]. Aricha-Tamir et al. [63] compared pregnancies before and after undergoing BS in the same women and found a significant reduction in hypertensive disorders in their postoperative pregnancies (adjusted OR 0.4, CI 0.2–0.8). Bennett et al. [60] reported that women who delivered following BS had significantly lower rates of preeclampsia and eclampsia (OR 0.20, CI 0.09–0.44), chronic hypertension complicating pregnancy

Table 17.2 Selected studies on pregnancy induced hypertension (PIH) before and after bariatric surgery (BS)

Study	Cases (pregnancies)	Controls (pregnancies)	Type of BS	Cases (%)	Controls (%)	OR	95% CI	Comments
Sheiner et al. [51] 2004, Israel	298	158,912	BS			NS	NS	Compared to general obstetric population
Bologolovkin et al. [47] 2012, USA	293	656,353	BS	NR	NR	NS	NS	Compared to general obstetric population
Josefsson et al. [53] 2011, Sweden	126	188,500	BS	1.6	1.1	NS	NS	Compared to general obstetric population
Dixon et al. [52] 2005, Australia	79	40 pre-surgery same women	LAGB	10	45	NR	NR	Lower incidence was significant (P Value <0.01) when compared to pre-surgery and matched BMI deliveries
		79 matched for BMI			38	NR	NR	
		Community			10–13	NS	NS	
Weintraub et al. [62] 2008, Israel	507	301	BS	11.2	23.6	0.4	0.3–0.6	Protective also for Severe PET (OR 0.2, 95% CI 0.1–0.7)
Bennett et al. [60] 2010, USA	316	269	BS	2.5	13.0	0.16	0.07–0.37	Reduced risk significant for all hypertensive disorders
Lapolla et al. [57] 2010, Italy	83	120 BMI $\geq$ 40	LAGB	9.6	23.5	0.77	0.60–0.99	PIH rates **higher** compared to normal BMI controls and **lower** compared to morbidly obese controls
		858 normal BMI			2.4	1.27	1.01–1.59	
	27	27 pre-surgery - same women		33.0	14.8	NS	NS	
Sheiner et al. [78] 2011, Israel	104 < 1st post-op year	358 > 1st post-op year	BS	15.4	11.2	NS	NS	
Aricha-Tamir et al. [63] 2011, Israel	144	144	BS	16.7	31.9	0.4	0.2–0.7	Reduced risk significant for all hypertensive disorders
Amsalem et al. [64] 2013, Israel	109	109	Restrictive (LAGB, SRVG)	7.4	21.0	0.3	0.12–0.82	Reduced risk significant also for second pregnancy following BS
Berlac et al. [75] 2014, Denmark	415	827 obese	RYGB	4.6	6.3	NR	NR	
		829 normal weight			1.8	NR	NR	
Adams et al. [61] 2015, USA	295	295	RYGB	4.4	11.9	0.31	0.14–0.65	

BS Bariatric surgery; *LAGB* Laparoscopic adjustable gastric banding; *SRVG* Silastic ring vertical gastroplasty; *RYGB* Roux-en-Y gastric bypass; *NS* No significant difference; *NR* Not reported; *BMI* Body mass index; PET = Pre-eclamptic Toxemia

(0.39, CI 0.20–0.74), and gestational hypertension (0.16, CI 0.07–0.37). These lower rates remained significant even after adjustment for age at delivery, surgical procedure, and preexisting diabetes. Additionally, Amsalem et al. [64] showed that the lower rates of hypertensive disorders remained significant even in the second pregnancy following BS.

In comparison to the general population, studies comparing risks for hypertensive disorders in the postoperative group found that the incidence of preeclampsia may decrease to approximate that of the general obstetrical community [51, 89, 90].

These lower rates of gestational hypertension and preeclampsia are important because hypertensive disorders of pregnancy may lead to intrauterine growth restriction and preterm deliveries, which are known risk factors for perinatal morbidity and mortality.

Prematurity

To date, it is still unclear whether pregnancies following BS carry an additional risk for preterm delivery as the data on the subject is confusing. After reviewing the literature, the largest trial examining prematurity after BS was published by Roos et al. [91] and reported a significantly increased rate of preterm deliveries but with no difference in perinatal mortality. A majority of other studies show no statistical difference in the risk for preterm deliveries, [52, 53, 56–59, 62, 92–94] and, according to a recent meta-analysis published by Yi et al. [74] examining eight studies including Roos et al., the mentioned study contributed a weight of 81% to the analysis. When this single study was omitted, there was no longer a significant difference. A different meta-analysis by Galazis [66] examining 12 studies found a 28% increase in preterm birth in post-surgery pregnancies. However, this result is again not in accordance with an older meta-analysis by Maggard et al. [67].

Fetal Growth

Obese and diabetic mothers are more likely to have macrosomic infants. Observational studies have generally reported a reduction in mean birthweight resulting in a larger proportion of appropriate for gestational age (AGA) infants among post-BS pregnancies compared with obese women who have not undergone a bariatric procedure [62, 92, 94, 95]. By now, it is evident that BS lowers the risk for macrosomia in post-bariatric pregnancy as almost all studies [53, 56, 59, 62, 67, 94, 96, 97], including some meta-analysis on the subject [66, 74], found decreased incidence of LGA infants. This finding is encouraging. However, even a risk for small neonates is a matter of concern. Some studies found no significant difference in rates of intrauterine growth restriction (IUGR) and small for gestational age (SGA) neonates [51] after specifically controlling for other variables such as obesity and hypertensive disorders. Data on IUGR and SGA should be carefully interpreted due to residual confounders in the studied groups. Nevertheless, evidence from larger controlled studies provides a different picture. The largest population-based cohort study, which included 670 women who underwent BS, reported a higher risk of SGA infants in the women who underwent surgery as compared with controls (16 vs. 8%, respectively) [55]. The control group was matched for pre-pregnancy BMI, age, parity, delivery year, and smoking status. A nationwide cohort study matched up to five births for every post-surgery birth and found clear increase in SGA neonates after BS [91]. More studies found similar results with up to 2.3 times higher risk for SGA infants [98] and even an adjusted odds ratio of 7.16 for SGA infants after gastric bypass procedure [99]. At least 3 meta-analysis [66, 74, 98] confirm the finding of increased risk for lower birth weight and SGA infants, and one estimates the risk to be increased by 80% [66]. The selected studies are summarized in Table 17.3.

It is postulated that the lower birth weights are a consequence of malnutrition caused by the postoperative state [70]. The risk for growth restriction appears to be particularly increased after mal-absorptive procedures [72] but might also be prevalent after restrictive procedures. As previously discussed, a subgroup analysis of four studies on women who underwent LAGB found no increased

Table 17.3 Selected studies on birth weight (Macrosomia, LGA and SGA) in pregnancy before and after bariatric surgery (BS)

Study	Cases (pregnancies)	Controls (pregnancies)	Type of BS	Cases (%)	Controls (%)	OR	95% CI	Comments
Sheiner et al. [51] 2004, Israel	298	158,912	BS			2.1	1.4–3.0	Higher risk for IUGR
Bologolovkin et al. [47] 2012, USA	293	656,353	BS	NR	NR	0.03	0.01–0.21	Higher risk for SGA (OR 2.69, 95% CI 1.96–3.69)
Weintraub et al. [62] 2008, Israel	507	301	LAGB	3.2	7.6	0.4	0.2–0.8	NS risk for SGA infants
Lesko et al. [58] 2012, USA	70	140	BS	4.3	18.1	0.21	0.06–0.71	Higher risk for SGA (OR 3.94, 95% CI 1.47–10.53)
Lapolla et al. [57] 2010, Italy	83	120 BMI $\geq$ 40	LAGB	8.1	9.4	NS	NS	Less LGA infants than obese controls NS risk for SGA infants
		858 normal BMI			6.0	NS	NS	
		27 pre-surgery - same women		4.2	16.0	NS	NS	
Aricha-Tamir et al. [63] 2011, Israel	144	144	BS	4.2	5.6	NS	NS	NS risk for IUGR
Amsalem et al. [64] 2013, Israel	109	109	Restrictive (LAGB, SRVG)	7.1	11.1	NS	NS	NS risk for IUGR
Kjaer et al. [97] 2013, Denmark	339	1277	BS	2.4	7.3	0.31	0.15–0.65	Higher risk for SGA (OR 2.29, 95% CI 1.33–3.96)
Johansson et al. [55] 2015, Sweden	597	2356	BS	8.6	22.4	0.33	0.24–0.44	Higher risk for SGA (OR 2.20, 95% CI 1.64–2.95)
Adams et al. [61] 2015, USA	295	295	RYGB	3.4	16.3	0.19	0.08–0.38	Higher risk for SGA (OR 2.16, 95% CI 1.00–5.04)

BS Bariatric surgery; *LAGB* Laparoscopic adjustable gastric banding; *SRVG* Silastic ring vertical gastroplasty; *RYGB* Roux-en-Y gastric bypass; *NS* No significant difference; *NR* Not reported; *BMI* Body mass index; Macrosomia = Birth weight >4500 g; *LGA* Large for gestational age (>90th percentile); *SGA* Small for gestational age (<10th percentile); *IUGR* Intrauterine growth restriction

risk for small neonates [66]. These results suggest that restrictive procedures might be preferred in obese women planning pregnancy after BS to avoid SGA.

Evidence strongly supports that BS successfully resolves macrosomia, but it at the expense of exposing fetuses to the risk of IUGR and lower birth weight. These pregnancies should be carefully monitored for fetal growth [98]. The combination of IUGR and prematurity (discussed before) for infants delivered post-surgery is a matter of concern and should be taken under consideration when following this unique group of post-bariatric pregnancies. However, it is important to emphasize that in most of the above mentioned studies examining fetal weight, overall perinatal mortality was not increased.

Cesarean Delivery

Obesity is a well-established risk factor for cesarean delivery (CD) [9]. Whether BS is a risk factor for CD is not clear as there is considerable variability in the literature. When compared to the general or non-obese populations, observational studies found patients after BS to have higher rates of CD [51, 62, 92], but this finding was not significant when comparing to obese or severely obese controls [57, 92, 97]. The latest ACOG Practice Bulletin on BS and Pregnancy states that CD rates are higher after BS, as high as 62% in one study [77]. However, two recent meta-analyses failed to show any significant difference in the rates of CD after BS as compared to obese counterparts [66, 74], and stated that CD was common in both groups. One study by Burke et al. [54] even found a CD rates were halved in post-BS patients compared to obese controls. As seen in Table 17.4, no strong relationship between CD and BS was demonstrated. Further research is still needed.

One possible explanation for higher rates of CD is that women who undergo BS are typically older and more likely to be obese than women in the general obstetrical population [76, 100]. Another explanation for this confounding data might lie in the indications for CD. On the one hand, we have shown that BS leads to lower rates of macrosomic infants that might lead to lower indicated CD, but on the other hand, post-bariatric parturient are generally older and have had a previous CD which might explain the higher rates of CD after BS in other studies. Importantly, the latest ACOG bulletin mentioned above [77] concludes that the BS itself should not be considered an indication for CD.

Perinatal Mortality

Previous BS is not associated with an increase in perinatal death. Encouragingly, most studies including a meta-analysis show no statistical difference in Apgar scores or perinatal mortality after BS [48, 51, 59, 66, 67, 97, 101]. Since most studies are still rather small, rare outcomes such as perinatal mortality is difficult to assess. Although some show a trend toward higher mortality, [54, 55] none were statistically significant. The largest study to date has statistically excluded a greater than double risk of neonatal mortality postoperatively [91]. In contrast, Weintraub et al. [62] studied 507 deliveries after BS and reported a decrease by half in perinatal mortality comparing to deliveries before surgery. A review of literature by Abodeely et al. [83] concluded that the risk of stillbirth after BS is either equal to or lower than the general population. Finally, the nationwide register study by Kjaer and colleagues [97] also found an adjusted odds ratio for perinatal death of 0.52 after BS although, once again, not statistically significant.

Post-bariatric Complications

Although risks of surgery are not reviewed in this chapter, special attention needs to be taken for post-surgery gastrointestinal activity and possible complications.

Table 17.4 Selected studies on cesarean deliveries (CD) in pregnancy before and after bariatric surgery (BS)

Study	Cases (pregnancies)	Controls (pregnancies)	Type of BS	Cases (%)	Controls (%)	OR	95% CI	Comments
Sheiner et al. [51] 2004, Israel	298	158,912	BS			2.4	1.9–3.1	
Bologolovkin et al. [47] 2012, USA	293	656,353	BS	NR	NR	1.34	1.06–1.69	Increasing risk with increasing levels of obesity
Weintraub et al. [62] 2008, Israel	507	301	LAGB	30.0	17.9	1.9	1.4–2.8	NS when controlling for previous CD
Santulli et al. [93] 2010, France	24	120 normal BMI	RYGB	33.3	16	NS	NS	Rate of CS before labor were higher in the post-op group compared to normal BMI controls
		120 matched BMI			34.2	NS	NS	
Lapolla et al. [57] 2010, Italy	83	120 BMI $\geq$ 40	LAGB	45.9	65.8	0.71	0.55–0.92	CD rates **higher** compared to normal BMI controls and **lower** compared to morbidly obese controls
		858 normal BMI			28.2	1.07	1.02–1.12	
	27	27 pre-surgery - same women		36.0	54.2	NS	NS	
Burke et al. [54] 2010, USA	354	346	BS	28	43	0.53	0.39–0.72	Significant even after adjusting for age and previous CD
Sheiner et al. [78] 2011, Israel	104 < 1st post-op year	358 > 1st post-op year	BS	36.5	30.4	NS	NS	
Aricha-Tamir et al. [63] 2011, Israel	144	144	BS	31.9	24.3	NS	NS	Main indications for CD in post-op group was previous CD (52%)
Lesko et al. [58] 2012, USA	70	140	BS	32.9	42.1	NS	NS	
Amsalem et al. [64] 2013, Israel	109	109	Restrictive (LAGB, SRVG)	30.6	27.8	NS	NS	NS also for second pregnancy following BS
Kjaer et al. [97] 2013, Denmark	339	1277	BS	32.7	28.7	NS	NS	NS also for subgroup analysis of women after LAGB
Adams et al. [61] 2015, USA	295	295	RYGB	35.9	41.4	NS	NS	

Bariatric surgery; *LAGB* Laparoscopic adjustable gastric banding; *SRVG* Silastic ring vertical gastroplasty; *RYGB* Roux-en-Y gastric bypass; *NS* No significant difference; *NR* Not reported; *BMI* Body mass index

Nutritional Deficiencies

Case studies have demonstrated nutritional deficiencies in postoperative pregnancies [52, 102–105] that could prevent a developing fetus from acquiring required nutrients. Procedures involving malabsorption, such as RYGB, appear more likely to cause nutritional deficiencies as compared to purely restrictive procedures such as LAGB.

Some studies have found a significant increase in maternal anemia in postoperative women [59, 62, 63] and Galazis's meta-analysis [66] supports this finding.

Mal-absorptive procedures are also prone to be associated with an increased risk of calcium, vitamin D, and vitamin B12 deficiencies [106]. Therefore, prenatal and perinatal oral iron treatments along with multivitamin, folate, and B12 supplementations are imperative.

Other nutrient deficiencies were reported as Eerdekens et al. [107] described five case reports of postoperative excessive vomiting or fat malabsorption that eventually resulted in severe vitamin K deficiency and fetal cerebral hemorrhage. Other case reports have described feto-maternal electrolyte imbalances [108] and microphthalmia attributed to vitamin A deficiency [109].

This potential for fetal congenital anomalies is a major concern as an association between BS and neural tube defects [NTD] was suggested in a number of case reports [110, 111] attributed to Folate deficiency. However, most research [51, 55, 62, 89] on the relationship between BS and fetal congenital anomalies was unable to find such association. The most reassuring finding on the subject was reported in a large study by Sheiner et al. [51] that found no difference in risk for congenital anomalies in post-bariatric patients comparing to the general population. This study was powered enough to conclude that no differences were found.

Nevertheless, In light of previous findings, regardless of the type of bariatric procedure, pre-conception counseling, routine nutritional screening, recommendations for appropriate supplements, and monitoring compliance of this unique population are needed.

Gastrointestinal Complications

Some life-threatening surgical complications of BS in post-bariatric parturients might be confused with pregnancy-related symptoms such as abdominal pain, hyperemesis and esophageal reflux. These complications could be difficult for obstetricians to recognize.

Bowel obstruction during pregnancy in post-bariatric women was reported in several case reports, and few resulted with fetal and maternal death [112, 113]. Most cases are attributed to bowel ischemia and internal hernia formation after RYGB [113–116]. The estimated prevalence of this complication is up to 2%, and it is contributed by elevated abdominal pressure and cephalad intestinal displacement caused by the enlarging gravid uterus [113]. Computed tomography scan and even exploratory surgery may be necessary in highly suspicious clinical circumstances [81, 117].

Among women who have undergone LAGB, band slippage may appear [118], especially if time interval between surgery and pregnancy is short [119–121]; nevertheless, as other post-bariatric surgical complications, systematic studies failed to reported high rates of this complication. Haward et al. [121] demonstrated that pregnancy does not increase the risk of primary or overall band revision after LAGB. Pilone et al. [122] also stated that band loosening should be reserved to symptomatic patients only and concluded that LAGB is a safe procedure, well tolerated during pregnancy, and without negative implications on both the mother and the baby.

Conclusions

In conclusion, while obesity is associated with adverse pregnancy outcome and mainly GDM, preeclampsia, and macrosomia, BS lowers incidence of GDM in following pregnancies and achieves overall improved outcomes for the mother and child. It is of great importance to consult obese women at reproductive age for weight reduction prior to conception and offering BS can be a reasonable alternative. One must keep in mind the post-surgery gastrointestinal complications, while they seem rare, some might be life-threatening. Pre-conception counseling regarding appropriate diet and nutritional supplementation is strongly advised and careful monitoring for fetal growth is recommended.

Guideline Recommendations

Women with lower BMIs are less likely to have GDM and the negative maternal and fetal outcomes associated with it. Clearly, preventing overweight and obesity is ideal, but until public health programs can be instituted overweight and obese women need treatment on an individual basis.

(1) BS is indicated for anyone with a BMI > 40 or a BMI > 35 with associated medical comorbidities (such as uncontrolled diabetes or hypertensive disorders) who has failed weight loss with conservative measures.
(2) Even though conventional medical weight loss has low success rates, a clinical judgment with higher threshold for BS should exist for young patients who are highly motivated to lose weight.
(3) Conversely, lower threshold should exist for older patients where limited fertile years may take precedence over the ability to lose weight.
(4) GCT may not be an appropriate screening test for women post mal-absorptive BS. Instead, HbA1C, fasting blood glucose, and postprandial blood glucose may be better measures in the second trimester. GCT remains an appropriate test to identify GDM in women post-restrictive BS.
(5) It is recommended to delay pregnancy for at least 1 year after surgery. Nevertheless, patients who became pregnant before or after 12 months post-surgery had similar outcomes. Accordingly, after careful consultation with the obstetrician and the bariatric surgeon, a shorter interval may be considered, with a careful follow-up during pregnancy.
(6) Post-restrictive BS pregnant women may need extra supplementation in calcium, vitamin D, vitamin B12, and folate. Dietary consultation is extremely important especially for patients following mal-absorptive procedures.
(7) BS by itself is not an indication for CD.

References

1. WHO. Obesity and overweight. Fact sheet No. 311. Updated January 2015. WHO.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311(8):806–14.
3. Dalenius K, Brindley P, Smith B, Reinold C, Grummer-Strawn L. Pregnancy Nutrition Surveillance 2010 Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2012.
4. Mission JF, Marshall NE, Caughey AB. Obesity in pregnancy: a big problem and getting bigger. Obstet Gynecol Surv. 2013;68(5):389–99.

5. Gunatilake RP, Perlow JH. Obesity and pregnancy: clinical management of the obese gravida. Am J Obstet Gynecol. 2011;204(2):106–19.
6. Burstein E, Levy A, Mazor M, Wiznitzer A, Sheiner E. Pregnancy outcome among obese women: a prospective study. Am J Perinatol. 2008;25(9):561–6.
7. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070–6.
8. Chu SY, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, Curtis KM. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obes Rev. 2007;8(5):385–94.
9. Sheiner E, Levy A, Menes TS, Silverberg D, Katz M, Mazor M. Maternal obesity as an independent risk factor for caesarean delivery. Paediatr Perinat Epidemiol. 2004;18(3):196–201.
10. Cnattingius S, Bergström R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med. 1998;338(3):147–52.
11. Driul L, Cacciaguerra G, Citossi A, Martina MD, Peressini L, Marchesoni D. Prepregnancy body mass index and adverse pregnancy outcomes. Arch Gynecol Obstet. 2008;278(1):23–6.
12. Schummers L, Hutcheon JA, Bodnar LM, Lieberman E, Himes KP. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. Obstet Gynecol. 2015;125(1):133–43.
13. Group HSCR. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Int J Gynaecol Obstet. 2002;78(1):69–77.
14. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD and others. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358(19): 1991–2002.
15. Yogev C, Hod C, Oats M, Metzger L, Dyer D and others. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. Am J Obstet Gynecol 2010;202(3):255.e1–7.
16. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, Lowe LP, Trimble ER, Coustan DR, Hadden DR and others. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012;35(4):780–6.
17. Yaniv-Salem S, Shoham-Vardi I, Kessous R, Pariente G, Sergienko R, Sheiner E. Obesity in pregnancy: what's next? Long-term cardiovascular morbidity in a follow-up period of more than a decade. J Matern Fetal Neonatal Med. 2016;29(4):619–23.
18. Kessous R, Shoham-Vardi I, Pariente G, Sherf M, Sheiner E. An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity. Heart. 2013;99(15):1118–21.
19. Beharier O, Shoham-Vardi I, Pariente G, Sergienko R, Kessous R, Baumfeld Y, Szaingurten-Solodkin I, Sheiner E. Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease. J Clin Endocrinol Metab. 2015;100(4):1412–6.
20. Sasson I, Beharier O, Sergienko R, Szaingurten-Solodkin I, Kessous R, Belfair NJ, Sheiner E. Obesity during pregnancy and long-term risk for ophthalmic morbidity—a population-based study with a follow-up of more than a decade. J Matern Fetal Neonatal Med 2015;1–5.
21. Kessous R, Davidson E, Meirovitz M, Sergienko R, Sheiner E. Prepregnancy obesity: a risk factor for future development of ovarian and breast cancer. Eur J Cancer Prev 2016.
22. Blank A, Grave GD, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed. Report of the international workshop on adverse perinatal outcomes of Gestational Diabetes Mellitus, December 3–4, 1992. Diabetes Care. 1995;18(1):127–9.
23. Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J. Gestational diabetes mellitus. A survey of perinatal complications in the 1980s. Diabetes. 1991;40(Suppl 2):74–8.
24. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3):e290–6.
25. Malcolm JC, Lawson ML, Gaboury I, Lough G, Keely E. Glucose tolerance of offspring of mother with gestational diabetes mellitus in a low-risk population. Diabet Med. 2006;23(5):565–70.
26. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics. 2003;111(3):e221–6.
27. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to fetal hyperinsulinism. Diabetes Care. 1995;18(5):611–7.
28. Catalano PM. Management of obesity in pregnancy. Obstet Gynecol. 2007;109(2 Pt 1):419–33.
29. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. Surgery 2007;142(4):621–32; discussion 632–5.
30. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.

31. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE and others. Bariatric surgery versus intensive medical therapy for diabetes–3-year outcomes. N Engl J Med 2014;370(21):2002–13.
32. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G and others. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366(17):1577–85.
33. Johnson EE, Simpson AN, Harvey JB, Simpson KN. Bariatric surgery implementation trends in the USA from 2002 to 2012. Implement Sci. 2016;11(1):21.
34. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, Yashkov Y, Frühbeck G, (IFSO-EC) IFfSoOaMD-EC, (EASO) EAftSoO and others. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 2014;24(1):42–55.
35. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724–37.
36. Hopkins JC, Blazeby JM, Rogers CA, Welbourn R. The use of adjustable gastric bands for management of severe and complex obesity. Br Med Bull 2016.
37. Schauer PR, Schirmer BD, Brethauer SA. Minimally Invasive Bariatric Surgery. New York, NY: Springer; 2007. p. 189.
38. Falk V, Twells L, Gregory D, Murphy R, Smith C, Boone D, Pace D. Laparoscopic sleeve gastrectomy at a new bariatric surgery centre in Canada: 30-day complication rates using the Clavien-Dindo classification. Can J Surg. 2016;59(2):93–7.
39. Brethauer SA, Hammel JP, Schauer PR. Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. Surg Obes Relat Dis. 2009;5(4):469–75.
40. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232(4):515–29.
41. Spivak H, Abdelmelek MF, Beltran OR, Ng AW, Kitahama S. Long-term outcomes of laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass in the United States. Surg Endosc. 2012;26(7): 1909–19.
42. Magro DO, Geloneze B, Delfini R, Pareja BC, Callejas F, Pareja JC. Long-term weight regain after gastric bypass: a 5-year prospective study. Obes Surg. 2008;18(6):648–51.
43. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. Ann Surg. 2006;244(5):734–40.
44. Sheiner E, Balaban E, Dreiher J, Levi I, Levy A. Pregnancy outcome in patients following different types of bariatric surgeries. Obes Surg. 2009;19(9):1286–92.
45. Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, Stampfer MJ, Speizer FE, Spiegelman D, Manson JE. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA. 1997;278(13):1078–83.
46. Hedderson MM, Williams MA, Holt VL, Weiss NS, Ferrara A. Body mass index and weight gain prior to pregnancy and risk of gestational diabetes mellitus. Am J Obstet Gynecol 2008;198(4):409. e1–7.
47. Belogolovkin V, Salihu HM, Weldeselasse H, Biroscak BJ, August EM, Mbah AK, Alio AP. Impact of prior bariatric surgery on maternal and fetal outcomes among obese and non-obese mothers. Arch Gynecol Obstet. 2012;285(5):1211–8.
48. Karmon A, Sheiner E. Pregnancy after bariatric surgery: a comprehensive review. Arch Gynecol Obstet. 2008;277(5):381–8.
49. Bar-Zohar D, Azem F, Klausner J, Abu-Abeid S. Pregnancy after laparoscopic adjustable gastric banding: perinatal outcome is favorable also for women with relatively high gestational weight gain. Surg Endosc. 2006;20 (10):1580–3.
50. Skull AJ, Slater GH, Duncombe JE, Fielding GA. Laparoscopic adjustable banding in pregnancy: safety, patient tolerance and effect on obesity-related pregnancy outcomes. Obes Surg. 2004;14(2):230–5.
51. Sheiner E, Levy A, Silverberg D, Menes TS, Levy I, Katz M, Mazor M. Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. Am J Obstet Gynecol. 2004;190(5):1335–40.
52. Dixon JB, Dixon ME, O'Brien PE. Birth outcomes in obese women after laparoscopic adjustable gastric banding. Obstet Gynecol. 2005;106(5 Pt 1):965–72.
53. Josefsson A, Blomberg M, Bladh M, Frederiksen SG, Sydsjö G. Bariatric surgery in a national cohort of women: sociodemographics and obstetric outcomes. Am J Obstet Gynecol 2011;205(3):206.e1–8.
54. Burke AE, Bennett WL, Jamshidi RM, Gilson MM, Clark JM, Segal JB, Shore AD, Magnuson TH, Dominici F, Wu AW and others. Reduced incidence of gestational diabetes with bariatric surgery. J Am Coll Surg 2010; 211(2):169–75.
55. Johansson K, Cnattingius S, Näslund I, Roos N. Trolle Lagerros Y, Granath F, Stephansson O, Neovius M. Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015;372(9):814–24.

56. Ducarme G, Revaux A, Rodrigues A, Aissaoui F, Pharisien I, Uzan M. Obstetric outcome following laparoscopic adjustable gastric banding. Int J Gynaecol Obstet. 2007;98(3):244–7.
57. Lapolla A, Marangon M, Dalfrà MG, Segato G, De Luca M, Fedele D, Favretti F, Enzi G, Busetto L. Pregnancy outcome in morbidly obese women before and after laparoscopic gastric banding. Obes Surg. 2010;20(9):1251–7.
58. Lesko J, Peaceman A. Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. Obstet Gynecol. 2012;119(3):547–54.
59. Shai D, Shoham-Vardi I, Amsalem D, Silverberg D, Levi I, Sheiner E. Pregnancy outcome of patients following bariatric surgery as compared with obese women: a population-based study. J Matern Fetal Neonatal Med. 2014;27(3):275–8.
60. Bennett WL, Gilson MM, Jamshidi R, Burke AE, Segal JB, Steele KE, Makary MA, Clark JM. Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data. BMJ. 2010;340: c1662.
61. Adams TD, Hammoud AO, Davidson LE, Laferrère B, Fraser A, Stanford JB, Hashibe M, Greenwood JL, Kim J, Taylor D and others. Maternal and neonatal outcomes for pregnancies before and after gastric bypass surgery. Int J Obes (Lond) 2015;39(4):686–94.
62. Weintraub AY, Levy A, Levi I, Mazor M, Wiznitzer A, Sheiner E. Effect of bariatric surgery on pregnancy outcome. Int J Gynaecol Obstet. 2008;103(3):246–51.
63. Aricha-Tamir B, Weintraub AY, Levi I, Sheiner E. Downsizing pregnancy complications: a study of paired pregnancy outcomes before and after bariatric surgery. Surg Obes Relat Dis. 2012;8(4):434–9.
64. Amsalem D, Aricha-Tamir B, Levi I, Shai D, Sheiner E. Obstetric outcomes after restrictive bariatric surgery: what happens after 2 consecutive pregnancies? Surg Obes Relat Dis. 2014;10(3):445–9.
65. Wittgrove AC, Jester L, Wittgrove P, Clark GW. Pregnancy following gastric bypass for morbid obesity. Obes Surg 1998;8(4):461–4; discussion 465–6.
66. Galazis N, Docheva N, Simillis C, Nicolaides KH. Maternal and neonatal outcomes in women undergoing bariatric surgery: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014;181:45–53.
67. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, Hilton L, Santry HP, Morton JM, Livingston EH and others. Pregnancy and fertility following bariatric surgery: a systematic review. JAMA 2008;300(19):2286–96.
68. Kominiarek MA. Preparing for and managing a pregnancy after bariatric surgery. Semin Perinatol. 2011;35 (6):356–61.
69. Vrebosch L, Bel S, Vansant G, Guelinckx I, Devlieger R. Maternal and neonatal outcome after laparoscopic adjustable gastric banding: a systematic review. Obes Surg. 2012;22(10):1568–79.
70. Sheiner E, Willis K, Yogev Y. Bariatric surgery: impact on pregnancy outcomes. Curr Diab Rep. 2013;13(1): 19–26.
71. Willis K, Sheiner E. Bariatric surgery and pregnancy: the magical solution? J Perinat Med. 2013;41(2):133–40.
72. Willis K, Alexander C, Sheiner E. Bariatric surgery and the pregnancy complicated by gestational diabetes. Curr Diab Rep. 2016;16(4):21.
73. Willis K, Lieberman N, Sheiner E. Pregnancy and neonatal outcome after bariatric surgery. Best Pract Res Clin Obstet Gynaecol. 2015;29(1):133–44.
74. Yi XY, Li QF, Zhang J, Wang ZH. A meta-analysis of maternal and fetal outcomes of pregnancy after bariatric surgery. Int J Gynaecol Obstet. 2015;130(1):3–9.
75. Berlac JF, Skovlund CW, Lidegaard O. Obstetrical and neonatal outcomes in women following gastric bypass: a Danish national cohort study. Acta Obstet Gynecol Scand. 2014;93(5):447–53.
76. Sheiner E, Menes TS, Silverberg D, Abramowicz JS, Levy I, Katz M, Mazor M, Levy A. Pregnancy outcome of patients with gestational diabetes mellitus following bariatric surgery. Am J Obstet Gynecol. 2006;194(2):431–5.
77. Gynecologists ACoOa. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol 2009;113(6):1405–13.
78. Sheiner E, Edri A, Balaban E, Levi I, Aricha-Tamir B. Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery. Am J Obstet Gynecol 2011;204(1):50.e1–6.
79. Andrade HF, Pedrosa W, Diniz MF, Passos VM. Adverse effects during the oral glucose tolerance test in post-bariatric surgery patients. Arch Endocrinol Metab 2016.
80. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Sugarman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA and others. Meta-analysis: surgical treatment of obesity. Ann Intern Med 2005; 142(7):547–59.
81. Wax JR, Pinette MG, Cartin A, Blackstone J. Female reproductive issues following bariatric surgery. Obstet Gynecol Surv. 2007;62(9):595–604.
82. Bonis C, Lorenzini F, Bertrand M, Parant O, Gourdy P, Vaurs C, Cazals L, Ritz P, Hanaire H. Glucose profiles in pregnant women after a gastric bypass: findings from continuous glucose monitoring. Obes Surg 2016.
83. Abodeely A, Roye GD, Harrington DT, Cioffi WG. Pregnancy outcomes after bariatric surgery: maternal, fetal, and infant implications. Surg Obes Relat Dis. 2008;4(3):464–71.

84. Ehrenthal DB, Jurkovitz C, Hoffman M, Jiang X, Weintraub WS. Prepregnancy body mass index as an independent risk factor for pregnancy-induced hypertension. J Womens Health (Larchmt). 2011;20(1):67–72.
85. Dennedy MC, Avalos G, O'Reilly MW, O'Sullivan EP, Dunne FP. The impact of maternal obesity on gestational outcomes. Ir Med J. 2012;105(5 Suppl):23–5.
86. Robinson HE, O'Connell CM, Joseph KS, McLeod NL. Maternal outcomes in pregnancies complicated by obesity. Obstet Gynecol. 2005;106(6):1357–64.
87. Sibai BM, Ewell M, Levine RJ, Klebanoff MA, Esterlitz J, Catalano PM, Goldenberg RL, Joffe G. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) study group. Am J Obstet Gynecol. 1997;177(5):1003–10.
88. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007; 357(8):741–52.
89. Wax JR, Cartin A, Wolff R, Lepich S, Pinette MG, Blackstone J. Pregnancy following gastric bypass for morbid obesity: effect of surgery-to-conception interval on maternal and neonatal outcomes. Obes Surg. 2008; 18(12):1517–21.
90. Dixon JB, Dixon ME, O'Brien PE. Pregnancy after Lap-Band surgery: management of the band to achieve healthy weight outcomes. Obes Surg. 2001;11(1):59–65.
91. Roos N, Neovius M, Cnattingius S, Trolle Lagerros Y, Sääf M, Granath F, Stephansson O. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. BMJ 2013;347:f6460.
92. Patel JA, Patel NA, Thomas RL, Nelms JK, Colella JJ. Pregnancy outcomes after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2008;4(1):39–45.
93. Santulli P, Mandelbrot L, Facchiano E, Dussaux C, Ceccaldi PF, Ledoux S, Msika S. Obstetrical and neonatal outcomes of pregnancies following gastric bypass surgery: a retrospective cohort study in a French referral centre. Obes Surg. 2010;20(11):1501–8.
94. Marceau P, Kaufman D, Biron S, Hould FS, Lebel S, Marceau S, Kral JG. Outcome of pregnancies after biliopancreatic diversion. Obes Surg. 2004;14(3):318–24.
95. Richards DS, Miller DK, Goodman GN. Pregnancy after gastric bypass for morbid obesity. J Reprod Med. 1987;32(3):172–6.
96. Ducarme G, Parisio L, Santulli P, Carbillon L, Mandelbrot L, Luton D. Neonatal outcomes in pregnancies after bariatric surgery: a retrospective multi-centric cohort study in three French referral centers. J Matern Fetal Neonatal Med. 2013;26(3):275–8.
97. Kjær MM, Lauenborg J, Breum BM, Nilas L. The risk of adverse pregnancy outcome after bariatric surgery: a nationwide register-based matched cohort study. Am J Obstet Gynecol 2013;208(6):464.e1–5.
98. Kjaer MM, Nilas L. Pregnancy after bariatric surgery–a review of benefits and risks. Acta Obstet Gynecol Scand. 2013;92(3):264–71.
99. Chevrot A, Kayem G, Coupaye M, Lesage N, Msika S, Mandelbrot L. Impact of bariatric surgery on fetal growth restriction: experience of a perinatal and bariatric surgery center. Am J Obstet Gynecol 2015.
100. Wax JR, Cartin A, Wolff R, Lepich S, Pinette MG, Blackstone J. Pregnancy following gastric bypass surgery for morbid obesity: maternal and neonatal outcomes. Obes Surg. 2008;18(5):540–4.
101. Josefsson A, Bladh M, Wiréhn AB, Sydsjö G. Risk for congenital malformations in offspring of women who have undergone bariatric surgery. A national cohort. BJOG. 2013;120(12):1477–82.
102. Guelinckx I, Devlieger R, Vansant G. Reproductive outcome after bariatric surgery: a critical review. Hum Reprod Update. 2009;15(2):189–201.
103. Dixon JB, Dixon ME, O'Brien PE. Elevated homocysteine levels with weight loss after lap-band surgery: higher folate and vitamin B12 levels required to maintain homocysteine level. Int J Obes Relat Metab Disord. 2001; 25(2):219–27.
104. Iavazzo C, Ntziora F, Rousos I, Paschalinopoulos D. Complications in pregnancy after bariatric surgery. Arch Gynecol Obstet. 2010;282(2):225–7.
105. Celiker MY, Chawla A. Congenital B12 deficiency following maternal gastric bypass. J Perinatol. 2009;29(9): 640–2.
106. Ziegler O, Sirveaux MA, Brunaud L, Reibel N, Quilliot D. Medical follow up after bariatric surgery: nutritional and drug issues. General recommendations for the prevention and treatment of nutritional deficiencies. Diabetes Metab 2009;35(6 Pt 2):544–57.
107. Eerdekens A, Debeer A, Van Hoey G, De Borger C, Sachar V, Guelinckx I, Devlieger R, Hanssens M, Vanhole C. Maternal bariatric surgery: adverse outcomes in neonates. Eur J Pediatr. 2010;169(2):191–6.
108. Weissman A, Hagay Z, Schachter M, Dreazen E. Severe maternal and fetal electrolyte imbalance in pregnancy after gastric surgery for morbid obesity. A case report. J Reprod Med. 1995;40(11):813–6.
109. Smets KJ, Barlow T, Vanhaesebrouck P. Maternal vitamin A deficiency and neonatal microphthalmia: complications of biliopancreatic diversion? Eur J Pediatr. 2006;165(7):502–4.

110. Pelizzo G, Nakib G, Alfei A, Iasci A, Cena H, Locatelli D, Mosconi M, Zappoli F, Calcaterra V. Fetal neural tube defects in pregnant women previously submitted to bariatric surgery: more attention to a new emerging entity. Prenat Diagn. 2013;33(2):196–7.
111. Moliterno JA, DiLuna ML, Sood S, Roberts KE, Duncan CC. Gastric bypass: a risk factor for neural tube defects? Case report. J Neurosurg Pediatr. 2008;1(5):406–9.
112. Loar PV, Sanchez-Ramos L, Kaunitz AM, Kerwin AJ, Diaz J. Maternal death caused by midgut volvulus after bariatric surgery. Am J Obstet Gynecol. 2005;193(5):1748–9.
113. Moore KA, Ouyang DW, Whang EE. Maternal and fetal deaths after gastric bypass surgery for morbid obesity. N Engl J Med. 2004;351(7):721–2.
114. Efthimiou E, Stein L, Court O, Christou N. Internal hernia after gastric bypass surgery during middle trimester pregnancy resulting in fetal loss: risk of internal hernia never ends. Surg Obes Relat Dis. 2009;5(3):378–80.
115. Kakarla N, Dailey C, Marino T, Shikora SA, Chelmow D. Pregnancy after gastric bypass surgery and internal hernia formation. Obstet Gynecol. 2005;105(5 Pt 2):1195–8.
116. Charles A, Domingo S, Goldfadden A, Fader J, Lampmann R, Mazzeo R. Small bowel ischemia after Roux-en-Y gastric bypass complicated by pregnancy: a case report. Am Surg. 2005;71(3):231–4.
117. Beard JH, Bell RL, Duffy AJ. Reproductive considerations and pregnancy after bariatric surgery: current evidence and recommendations. Obes Surg. 2008;18(8):1023–7.
118. Pilone V, Di Micco R, Monda A, Villamaina E, Gentile M, Forestieri P. LAGB in pregnancy: slippage after hyperemesis gravidarum. Report of a case. Ann Ital Chir 2012;83(5):429–32.
119. Van Mieghem T, Van Schoubroeck D, Depiere M, Debeer A, Hanssens M. Fetal cerebral hemorrhage caused by vitamin K deficiency after complicated bariatric surgery. Obstet Gynecol. 2008;112(2 Pt 2):434–6.
120. Kirshtein B, Lantsberg L, Mizrahi S, Avinoach E. Bariatric emergencies for non-bariatric surgeons: complications of laparoscopic gastric banding. Obes Surg. 2010;20(11):1468–78.
121. Haward RN, Brown WA, O'Brien PE. Does pregnancy increase the need for revisional surgery after laparoscopic adjustable gastric banding? Obes Surg. 2011;21(9):1362–9.
122. Pilone V, Hasani A, Di Micco R, Vitiello A, Monda A, Izzo G, Iacobelli L, Villamaina E, Forestieri P. Pregnancy after laparoscopic gastric banding: maternal and neonatal outcomes. Int J Surg. 2014;12(Suppl 1):S136–9.

Part VI
Dietary Interventions and Exercise

Chapter 18
Myo-Inositol Supplementation in Gestational Diabetes

Rosario D'Anna and Angelo Santamaria

Key Points

- Gestational Diabetes Mellitus rate is progressively growing in all Western countries, with a corresponding increasing mean body weight in young women.
- A syndrome like gestational diabetes which involves more than 10% of all pregnant women needs a primary prevention strategy.
- Data from studies in which a primary prevention was carried with diet or metformin are conflicting.
- Myo-inositol is a polyol involved in cellular glucose uptake acting as a second messenger of insulin message.
- In women at risk, a supplementation with myo-inositol showed a significant reduction in gestational diabetes rate.
- The effects of a myo-inositol supplementation on clinical outcomes are far from conclusive and need larger studies.

Keywords Gestational diabetes mellitus · Insulin resistance · Inositols · Myo-inositol · D-chiro-inositol

Abbreviations

IADPSG	International Association of the Diabetes and Pregnancy Study Groups
GDM	Gestational diabetes mellitus
CS	Caesarean section
PCOS	Polycystic ovary syndrome
MI	Myo-inositol
DCI	D-chiro-inositol
GPI	Glycosylphosphatidylinositol
IPGs	Inositol phosphoglycans
GLUT-4	Glucose Transporter Type 4
DM	Diabetes mellitus

R. D'Anna (✉) · A. Santamaria (✉)
Department of Human Pathology and Development, "Gaetano Martino" University Hospital, University of Messina, Messina, Italy
e-mail: rdanna@unime.it

A. Santamaria
e-mail: angelosantamaria83@alice.it

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_18

FSH	Follicle-stimulating hormone
LH	Luteneizing hormone
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
BMI	Body mass index

Introduction

From the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study data [1], the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published recommendations for the diagnosis and classification of hyperglycemia during pregnancy [2]. Since 2010, our group has diagnosed Gestational Diabetes Mellitus (GDM) according to these recommendations, later modified by the American Diabetes Association [3]: at 24–28 weeks of gestation with a 75-g 2-h glucose tolerance test using threshold values of 92 mg/dL or greater fasting, 180 mg/dL or greater 1 h post load, and 153 mg/dL or greater 2 h post load, at least one of the three values that exceeds or equals the threshold was diagnostic of GDM. In our setting, new criteria for diagnosing GDM has increased more than double the number of diagnosis, now totaling 12.5% of all deliveries in our University Hospital. It means that at the moment of the diagnosis (24–28 weeks gestation), the diabetic woman leaves the low-risk group, and she is included in the high-risk group, where obstetric evaluation and ultrasound examination are more frequent. Also the timing of delivery is different, following our guidelines labor is induced at 39 weeks gestation if she is treated with insulin or at 40 weeks gestation if she is treated only by diet. These strategies are useful in preventing GDM complications like macrosomia, shoulder dystocia, neonatal hypoglycemia, and distress respiratory syndrome. On the other hand, every new diagnosis of GDM means more cost for monitoring pregnancy, for drugs and for possible increased percentage of caesarean section (CS). We suspect that those who did not accept the new criteria for diagnosing GDM were worried about the risk of increased public health cost, but we think that the solution is not to hide GDM, but to prevent it. The first approach for the primary prevention of GDM is lifestyle, which means diet with or without physical exercise. There are a lot of studies on this issue, but the last Cochrane [4] stated that based on the data currently available there are no clear differences in the risk of developing GDM for women receiving a combined diet and exercise intervention compared to women receiving no intervention. Attempts to prevent GDM in infertile women affected by Polycystic Ovary Syndrome (PCOS) have been carried out with metformin, an insulin-sensitizing drug, but the results from those studies have been conflicting, especially between randomized and not randomized trials. In a recent meta-analysis [5], all these studies were reviewed until December 2013, and the result was that metformin did not affect GDM rate in PCOS women. Another substance: myo-inositol (MI), considered as a supplement, but with interesting insulin sensitizing effect has been used in the last years. In this review, we considered MI biology, sources and metabolism as well as its actual use in all the clinical conditions in which insulin resistance is present: PCOS, metabolic syndrome, and gestational diabetes.

Myo-Inositol

MI is a polyol, it is one of the nine stereo-isomeric forms of inositol, which is linked to phospholipids in the membranes of all living cells. It is produced by the human body from D-glucose, but we can find it in our food too. The greatest amounts of MI in common foods are found in fresh fruits and vegetables. Among the vegetables, the highest contents of MI are observed in beans and peas,

whereas among fruit, cantaloupe melons and citrus fruits have the highest content. In humans, the kidney is the most important organ in MI metabolism; in fact, each kidney produces about 2 g per day, more than daily dietary intake, which is about 1 g; and only in the kidneys MI is catabolized. Cells may supply themselves with inositol synthesizing it from glucose-6-phosphate, or from breakdown of inositol-containing membrane phospholipids, or with an uptake from the extracellular fluid via MI transporters [6]. In vivo conversion of MI to the other isomer D-chiro-inositol (DCI) can occur in tissues expressing the specific epimerase. Regarding glucose metabolism, MI and DCI are involved as components of glycosyl-phosphatidylinositol (GPI) and of inositol phosphoglycans (IPGs) that would constitute second messengers of insulin action in the GPI/IPG pathway. Furthermore, it has been shown that MI-PG and DCI-PG mediate different actions of insulin: MI-PG is involved in cellular glucose uptake via activation of Glucose Transporter Type 4 (GLUT-4) translocation to the plasma membranes and so enhancing glucose entry into the cells; whereas DCI-PG is involved in glycogen synthesis [7].

It has been shown that in human subjects diabetes mellitus (DM) is characterized by an imbalance between MI and DCI, with a decreased urinary excretion of DCI and an increased urinary excretion of MI [8]. These results suggest that in DM, a MI intracellular depletion occurs, probably caused by an inhibition of cellular MI uptake. Indeed, some experimental studies have shown that in hyperglycemic conditions, such as in DM, the glucose-induced MI uptake inhibition results from a competition between MI and glucose for MI transporters since MI and glucose exhibit structural similarities [9]. Therefore, high glucose concentration in the extracellular space could impair MI uptake and so contribute to the MI intracellular depletion observed in DM.

Depletion of intracellular MI and consequently decreased production of DCI from MI reduces the availability of these two substances for their incorporation into IPGs, putative second messengers of insulin. Indeed, in type 2 DM patients, a decreased IPG level in muscle biopsies as compared to healthy controls was demonstrated [8]. Therefore, the decreased inositol content in insulin target tissues could reduce insulin signal transduction involving IPGs and so further enhance or contribute to the insulin resistance in those tissues. All these considerations induced the authors of a recent review on MI to suggest a therapeutic use of MI and/or DCI supplementation in DM to restore depleted tissue levels of these two substances [10].

Therapeutic Use of Myo-Inositol

Therapeutic use of inositol isomers began probably with a paper of Nestler et al. [11], who published a study in which 1200 mg daily of DCI was administered to 22 obese PCOS women at least for 6 months. The results were amazing, and showed an improvement in ovarian function, and a decrease in blood pressure levels, but also in androgens and triglyceride concentrations. These preliminary results were not subsequently confirmed by the same group [12]; furthermore, during the study the drug DCI was withdrawn from the market, causing a discontinuation of the study. In the same years, some Italian groups started to use MI in infertile women affected by PCOS, obtaining encouraging results by improving metabolic and hormonal parameters. Indeed, MI supplementation restored spontaneous ovarian activity and consequently fertility, decreasing some hormones circulating levels such as Follicle Stimulating Hormone (FSH), Luteneizing Hormone (LH), and testosterone. These results were obtained by reducing insulin resistance, but also blood pressure, triglycerides, total and LDL cholesterol concentrations [10]. A possible answer to the question, asking why MI works where DCI failed in PCOS women, is suggested by a recent experimental study by the group of Larner [13], who demonstrated that in PCOS ovarian theca cells an increase of MI to DCI epimerase activity and

a decrease of MI/DCI ratio occurs, probably mediated by hyperinsulinaemia, which determines an overproduction of DCI, which lead to a deficiency of MI in the ovary. This paradoxical situation is, however, characteristic of the ovary, which is a non-insulin-resistant organ.

Another hyperinsulinemic pathological condition in which MI supplementation might be useful is the Metabolic Syndrome, especially in postmenopausal women. In a prospective, randomized, controlled trial, 40 postmenopausal women affected by Metabolic Syndrome were treated with 4 g MI daily plus folic acid for 6 months, obtaining a crucial reduction of insulin resistance, calculated by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR); but also a reduction of blood pressure levels together with a decrease in triglycerides and total cholesterol serum levels, and a significant improvement in LDL cholesterol [14].

Myo-Inositol and GDM

Prospective studies carried out by our group on MI in pregnancy for GDM prevention, began after a preliminary study in which MI was used in women with a diagnosis of GDM. It was a prospective, randomized, controlled trial [15], in which diet-treated women with GDM, diagnosed at 24–28 weeks gestation, were randomly assigned to receive either MI supplementation (4 g daily) plus folic acid (400 μg daily) or folic acid only (400 μg daily), as the control group. Both groups received the same diet prescription. Insulin resistance assessed by HOMA-IR and adiponectin, an insulin sensitizing substance produced by adipocytes, were assayed at the time of the diagnostic oral glucose tolerance test (OGTT) and after 8 weeks of treatment. HOMA-IR decreased in both groups (50% in the study group versus 29% in the control group), but the decline in the study group was significantly greater than that in the control group. Furthermore, adiponectin increased in the MI group while it decreased in the control group. Having shown that MI may reduce insulin resistance, whose increase is crucial in the pathogenesis of GDM, the next step was a MI supplementation from the first trimester, with the aim of preventing GDM onset. The result of a retrospective study [16], carried out on women affected by polycystic ovary syndrome (PCOS) reinforced our convincement. This study considered 2 groups of 98 infertile PCOS women treated with two different insulin sensitizing substances: myo-inositol or metformin, with the aim to obtain normal cycles and ovulation. After a first positive pregnancy test, metformin was stopped and this group was considered as a control group, whereas in the other group MI was continued throughout the whole pregnancy until delivery. From the patients' records, we registered the prevalence of GDM diagnosis performed after an OGTT at 24–28 weeks gestation. There was a significant difference in the rate of GDM diagnosis between the 2 groups: 17.4% in the MI group versus 54% in the control group [16]. Even if retrospectively, that study demonstrated that a MI supplementation, that began in the first trimester, might reduce GDM rate. Thus, we started 3 prospective, randomized, open label studies, controlled with placebo, to verify this hypothesis in different groups of women at risk: (a) a parent with type 2 diabetes [17]; (b) obese women: body mass index (BMI) $\geq$ 30 kg/m^2 [18]; (c) overweight women: BMI > 25 < 30 [19]. In all these studies, we used the same dosage: MI (2 g plus 200 mcg folic acid twice a day) or placebo (200 mcg folic acid twice a day) from the end of the first trimester until delivery; furthermore, the same number of women was involved: 110 in MI group and 110 in the placebo group. We calculated this number before the first trial, considering an expected rate of GDM less than 50% in the treated group, compared to the placebo group. Now, we know that the reduction was beyond our prudent expectation; in fact, in each study the rate of GDM reduction in the MI group was about 60% (Table 18.1). Results from 2 recent meta-analysis [20, 21] confirm that the prevalence of GDM was significantly decreased in the group treated with MI. This is the first important result of these studies, the reduction in GDM rate, which was the principal outcome, and it is worth noting that the reduction was the same in every study. What does it mean? How it is possible that MI works in the same way in different

Table 18.1 GDM prevalence in the 3 studies

Risk factors	My group (no. 301) (%)	Placebo group (no. 307) (%)	Reduction (%)
Family history of type 2 diabetes	6 = 6	15 = 15.3	−60
Obesity	15 = 14	36 = 33.6	−58.3
Overweight	11 = 11.6	28 = 27.4	−60.7
Overall	32 = 10.6	79 = 25.7	−59.5

kinds of women at risk for GDM? It seems that MI works independently from different metabolic conditions: a parent affected by type 2 diabetes or overweight until obesity. A BMI more than 25 is one of the most important risk factors for GDM, but in the first study [17], in the MI group, BMI was less than 23 and therefore only a genetic characteristic could be invoked to justify the risk. The rate of GDM diagnosis in the placebo group seems to confirm this hypothesis because the rate increases directly to the increase of BMI, reaching in the obese women almost 34% (Table 18.1). Only in the study involved obese women [18], insulin resistance expressed in HOMA-IR was calculated, highlighting a reduction from the first trimester to the time of OGTT, and we suppose that in this result there are the biochemical basis of the reduction in GDM rate. Another Italian group [22] performed a small prospective, randomized controlled study on women with another important risk factor, elevated first trimester fasting glucose (>100 mg/dl), reporting a reduced risk of developing GDM in the group treated with myo-inositol (Table 18.2).

Secondary outcomes in all the studies were the clinical outcomes. Prevalence of GDM complications was very low and different through the 3 studies, and whether 220 women were enough to demonstrate a reduction of GDM onset, the sample was underpowered to ascertain statistical significant differences in clinical outcomes. However, evaluating altogether the women from whom we have the records of their outcomes, we can consider 291 in the MI group and 304 in the placebo group. In Table 18.3, all clinical outcomes from the 3 studies are taken together and compared between groups. Performing the Student's test, for 2 of these outcomes the difference is significant: macrosomia and preterm birth (Table 18.3). Major complications as macrosomia, preterm birth, and gestational hypertension showed a prevalence in the MI group of about one-third compared to the placebo group, with a decrease of 65, 64, and 67% respectively, very similar to the reduction of GDM rate in the treated group, highlighting a direct correspondence between GDM onset and the prevalence of major complications. There was no difference between groups in the Caesarean Section (CS) rate, but in Italy, and in particular in the south of Italy, the indications for CS are not so strong and appropriate as in other European countries. Clinical outcomes were considered also in the

Table 18.2 GDM onset risk reduction in the MI group compared to the placebo group

Risk factors	MI group OR
Family history of type 2 diabetes	0.35
Obesity	0.34
Overweight	0.33
Fast glucose > 100 mg/dl	0.12

Table 18.3 Major clinical outcomes in the 3 studies

Outcomes	MI group (no. 291)	Control group (no. 304)	P
Macrosomia	6	16	0.04
Caesarean section	122 (41.9%)	140 (46.1%)	0.35
Preterm birth	10	23	0.03
Gestational hyper	4	12	0.07

2 meta-analyses, highlighting that birth weight and neonatal hypoglycemia were significantly decreased in the women treated with MI, but also each glucose level at the OGTT evaluation was significantly different compared to the control group [20]; instead, in the other, it was not demonstrated [21].

A qualified comment published by Coustan [23], one of the fathers of GDM screening, outlined the safety of MI supplementation, suggesting that it does not seem harmful for the mother and the fetus. Indeed, MI at the dose usually used is safe and well tolerated. Side effects, when present, are mild and mainly gastrointestinal like nausea, flatus, and diarrhea [24]. Furthermore, it is clearly assessed that MI transfer from the mother to the fetus is very low with no potential damage for the fetus.

In conclusion, this review on myo-inositol supplementation in women at risk for gestational diabetes may suggest that its use in the primary prevention of GDM seems to be promising, but larger, randomized, double blind studies are needed to confirm it.

References

1. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA, HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002.
2. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva AD, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care. 2010;33:676–82.
3. American Diabetes Association. Standards of medical care in diabetes-2011. Diab Care. 2011;34(suppl 1):s11–61.
4. Bain E, Crane M, Tieu J, Han S, Crowther CA, Middleton P. Diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Database Syst Rev. 2015;4:CD010443.
5. Zhuo Z, Wang A, Yu H. Effect of metformin intervention during pregnancy on the gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and meta-analysis. J Diab Res. 2014;381231.
6. Deranieh RM, Greenberg ML. Cellular consequences of inositol depletion. Biochem Soc Trans. 2009;37: 1099–103.
7. Dinicola S, Chiu TT, Unfer V, Carlomagno G, Bizzarri M. The Rationale of the myo-inositol and d-chiro-inositol combined treatment for polycystic ovary syndrome. J Clin Pharmacol. 2014;54:1079–92.
8. Kennington AS, Hill CR, Craig J, Bogardus C, Raz I, Ortmeyer HK, Hansen BC, Romero G, Larner J. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. N Engl J Med. 1990;323:373–8.
9. Haneda M, Kikkawa R, Arimura T, Ebata K, Togawa M, Maeda S, Sawada T, Horide N, Shigeta Y. Glucose inhibits myo-inositol uptake and reduces myoinositol content in cultured rat glomerular mesangial cells. Metab Clin Exp. 1990;39:40–5.
10. Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic disease. Biochimie. 2013;95:1811–27.
11. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. NEJM. 1999;340:1314–20.
12. Cheang KI, Baillargeon J-P, Essah PA, Ostlund RE, Apridonize T, Islam L, Nestler JE. Insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator correlates with insulin sensitivity in women with polycystic ovary syndrome. Metabolism. 2008;57:1390–7.
13. Heimark D, McAllister J, Larner J. Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls. Endocrine J. 2014;61:111–7.
14. Giordano D, Corrado F, Santamaria A, Quattrone S, Pintaudi B, Di Benedetto A, D'Anna R. Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome. A perspective, randomized, placebo-controlled study. Menopause. 2011;18:102–4.
15. Corrado F, D'Anna R, Di Vieste G, Giordano D, Pintaudi B, Santamaria A, Di Benedetto A. The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. Diabet Med. 2011;28:972–5.
16. D'Anna R, Benedetto V, Rizzo P, Raffone E, Interdonato ML, Corrado F, Di Benedetto A. Myo-inositol may prevent gestational diabetes in PCOS women. Gynecol Endocrinol. 2012;28:440–2.

17. D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, Corrado F, Di Benedetto A. Myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes. Diab Care. 2013;36:854–7.
18. D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, Neri I, Pintaudi B, Corrado F, Facchinetti F. Myo-inositol Supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol. 2015;126:310–5.
19. Santamaria A, Di Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, Neri I, Facchinetti F. Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. J Matern Fetal Neonatal Med. 2015;23:1–4.
20. Zheng X, Liu Z, Lin Y, Song J, Zheng L, Lin S. Relationship between myo-inositol supplementary and gestational diabetes mellitus: a meta-analysis. Med(Baltimore). 2015;94(42):e1604.
21. Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Cochrane Database Syst Rev. 2015;12:CD011507.
22. Matarrelli B, Vitacolonna E, D'Angelo M, Pavone G, Mattei PA, Liberati M, Celentano C. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized, controlled trial. J Matern Fetal Neonatal Med. 2013;26:967–72.
23. Coustan DR. Can a dietary supplement prevent gestational diabetes mellitus? Diab Care. 2013;36:777–9.
24. Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci. 2011;15:931–6.

Chapter 19
Treatments with Low Glycaemic Index Diets in Gestational Diabetes

Sangeetha Shyam and Amutha Ramadas

Key Points

- Gestational Diabetes Mellitus (GDM) is the carbohydrate intolerance that results from maternal inability to cope with increased insulin resistance associated with pregnancy.
- GDM management aims to achieve glycaemic control and promote adequate weight gain in the mother and also improve foetal outcomes.
- Diet is the cornerstone of GDM management.
- Low Glycaemic Index (GI) or glycaemic load (GL) diets by preventing postprandial glycaemic and insulinaemic peaks, attenuate cardiovascular risks; especially in subjects with obesity, insulin resistance or hyperinsulinaemia.
- Low-GI diets are beneficial only when they comply with current dietary guidelines and therefore require appropriate dietetic supervision.
- GDM subjects on low-GI diets have lower spikes in post-meal glycaemia and are less likely to require the initiation of insulin therapy when compared to those receiving standard diets with higher GI.
- Low-GI diets in GDM may also reduce central adiposity in the foetus.
- Low-GI diets are also likely to benefit GDM women in managing their glycaemia and body weight post-delivery.
- Current evidence raises no safety issues in using low-GI/GL diets in GDM management.
- However, further evidence is required to lend unequivocal support for the benefit of low-GI/GL diets in GDM treatment.

Keywords Gestational diabetes mellitus · Diet · Glycaemic index · Glycaemic load · Pregnancy

Abbreviations

GDM	Gestational diabetes mellitus
GI	Glycaemic index
GL	Glycaemic load
T2DM	Type 2 diabetes mellitus

S. Shyam (✉)
Division of Nutrition and Dietetics, School of Health Sciences, International Medical University, No. 126, Jalan Jalil Perkasa 19, 57000 Bukit Jalil, Kuala Lumpur, Malaysia
e-mail: sangeethashyam@imu.edu.my; sangeeshyam@gmail.com

A. Ramadas
Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Jalan Lagoon Selatan, 47500 Bandar Sunway, Selangor, Malaysia
e-mail: amutha.ramadas@monash.edu; amutha80@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_19

RCT Randomised-controlled trial
CVD Cardiovascular disease
SCFA Short-chain fatty acids

Introduction

Gestational Diabetes mellitus (GDM) is defined as the 'glucose intolerance first recognised during pregnancy' [1]. All pregnancies are accompanied by metabolic changes that promote adipose tissue accumulation in early gestation, followed by an increase in insulin resistance to provide adequate nourishment to the foetus [2]. The insulin resistance is accompanied by increased pancreatic insulin secretion to maintain maternal euglycaemia as the pregnancy progresses [2]. Hyperglycaemia results when the maternal insulin secretion is unable to meet the increased insulin demand [1, 3]. Therefore, the pathophysiology of GDM is similar to that of type 2 diabetes mellitus (T2DM); namely, marked insulin resistance and impairment of insulin secretion [4] and associated dyslipidaemia [5]. Thus management of postprandial glycaemia and insulin demand are essential targets for GDM management.

Diet is the cornerstone of GDM management [1, 6]. Dietary management for GDM has the following maternal goals: achieving glycaemic control, ensuring adequate weight gain and appropriate nutritional status. Achieving these goals ensures maternal and foetal health. More intensive medical management and increased surveillance are instituted in women who fail to respond adequately to diet therapy and increases treatment costs [7]. Most importantly, GDM increases long-term health risks for the mother and her offspring [1, 7] posing greater demand on healthcare resources.

Carbohydrates predominantly influence postprandial glycaemic response [8]. Therefore, carbohydrate restriction has historically been the prime focus of dietary management for GDM [1]. Restricting carbohydrates to provide around 45% of the energy is safe in GDM pregnancies [9], though evidence from randomised-controlled trials (RCTs) support the use of diets with reasonably high amount of complex carbohydrates [1]. Low-carbohydrate diets that are high in protein and fat intake, may increase risk for diabetes specifically among pregnant women [6] and can compromise foetal outcomes [7]. In the absence of concrete evidence to favour any particular diet, consensus panels for GDM have no specific recommendation but encourage the adoption of conventional healthy diets [1, 5].

As the role for low-carbohydrate diets is limited by their health concerns, the effect of carbohydrate quality (type) on glucose metabolism and insulin resistance has gathered interest [10]. Emerging evidence suggests that deterioration of glucose homeostasis can be prevented by monitoring both carbohydrate quantity and quality [10]. Concepts of glycaemic index (GI) and glycaemic load (GL) were born out of this need to describe the quality or type of carbohydrate foods.

This review aims to assess the current evidence for the treatment of GDM with low-GI/GL diets. The objective of this review is in-line with the professional societies' repeated calls for the consolidation of current evidence and efforts to bridge the knowledge deficits in this area to identify optimal diets for GDM women [5, 7, 11]. This is especially important because GDM affects a significant proportion of pregnant women globally, and alarmingly its prevalence is increasing [11].

Glycaemic Index (GI)

Carbohydrate foods even when consumed in equal amounts differ in their glycaemic effect. Hence physiological effects of carbohydrates are better described by their in vivo ability to raise blood glucose [12]. GI is such a physiological classification of carbohydrates [12], that ranks them on a scale of 0–100, in accordance to their postprandial glycaemic effect [13]. GI, therefore, reflects the rate of conversion of a carbohydrate into glucose [13]. Higher the GI value of a food, greater the postprandial glycaemic response it elicits [14] (Fig. 19.1).

The GI of a food is measured as 'the incremental area under the blood glucose response curve of a 50 g available carbohydrate portion of the food expressed as a percentage of the response after 50 g of glucose taken by the same subject' [14]. To simplify interpretation, foods are often classified into three categories based on their GI: high (GI >70), intermediate (GI between 55 and 70) and low (GI <55) [15].

Factors Affecting Glycaemic Index

The differences in GI of food depend on the type of sugar and or starch it contains [16], the extent of processing it has undergone [15] and the presence of factors that determine the rate of carbohydrate absorption [16]. Low-GI recommendations utilise these determinants to lower postprandial glucose responses.

Foods with a high content of fructose (fruits), and galactose (milk products) provide lower amounts of absorbable glucose, and thus have lower GI [16]. Beans and seeds have fibrous coats that slow down the access of enzymes to the starch inside [17, 18]. Beans and rolled oats are also rich in viscous fibre that delays gastric emptying [19], enzymatic starch hydrolysis [17] and consequently delay glucose absorption [19]. Basmati rice and legumes also contain a greater amylose: amylopectin ratio that slows down the rate of starch hydrolysis and glucose absorption [16]. The presence of organic acids in oranges [20] and legumes [18] reduce the rate of starch digestion and thereby elicit lower glycaemic responses. These foods are therefore recommended in low-GI diets. Small amounts

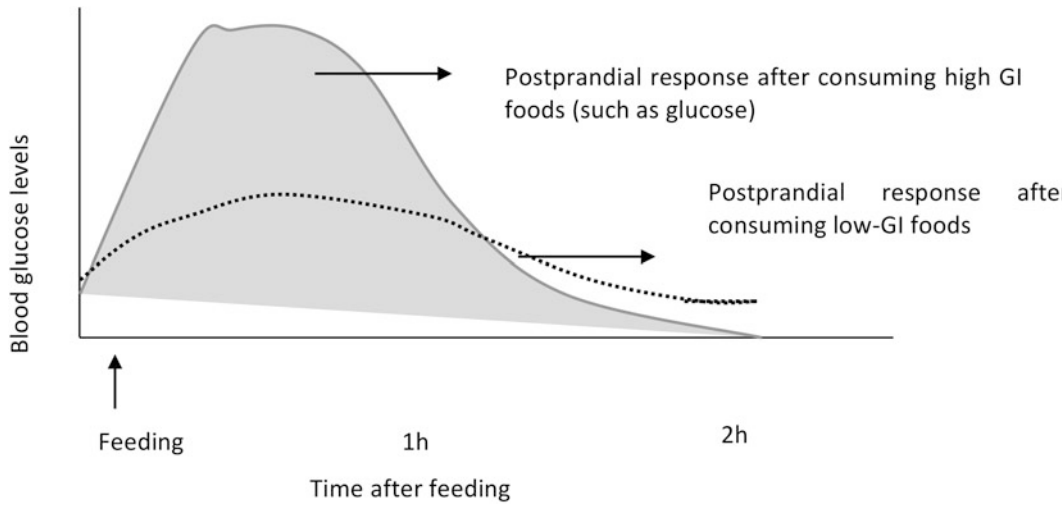


Fig. 19.1 Comparison of blood glucose *curves* after consumption of low- and high-GI foods. *Legend* GI: glycaemic index

of acetic acid (vinegar) when consumed along with the meal, reduces postprandial hyperglycaemia by 20% due to delayed gastric emptying and inhibition of digestive enzymes [21] and is a probable strategy to reduce meal GI. Furthermore, gelatinization of starch during heat treatment increases its availability to amylases and its GI [22]. Therefore, low-GI recommendations emphasise on the need to prevent overcooking of cereal foods like spaghetti and oatmeal.

Glycaemic Index of Mixed Meals

GI of individual foods in a meal has shown to predict the glycaemic response when eaten together [16] in different environments and for different cuisines [23]. The GI of a mixed meal is calculated as the sum of the proportional GI contributions of each carbohydrate component of the meal [16]. Daily diet GI is similarly calculated as the mean GI of meals consumed during the day [18].

A 15% reduction in dietary GI ($\sim$10 GI units for most populations) is thought to confer clinically significant health benefits [24, 25]. Given that staple cereals predominantly determine dietary GI, a 10 unit GI reduction is achieved by substituting usual high-GI staples with lower GI alternatives, while maintaining their prescribed serving size [26]. Another practical strategy to efficiently lower GI is to include one low-GI food in each meal, since GI works through the principle of averages [24]. A sample of dietary recommendations used to lower the GI of healthy diets is provided in Table 19.1.

Glycaemic Load (GL)

Due to its methodology of determination, GI may not reflect the glycaemic effect of a typical carbohydrate serving [27]. The glycaemic load (GL) concept was therefore invented to quantify the overall glycaemic effect of a portion of food [28]. The GL of a typical serving of food is the product of the amount of available carbohydrate it contains and its GI value [8]. GL of a serving is thus a measure of both carbohydrate quality and quantity [8] and accurately predicts postprandial glycaemia [29]. Accordingly, GL of a meal can be reduced either by reducing the amount of carbohydrate in diet, selecting foods that have lower GI or a combination of both [29] (Fig. 19.2).

While dietary GL can be reduced by different methods (Table 19.2), efforts that lower risks for T2DM [28] and cardiovascular disease (CVD) [3], reduce GL predominantly by lowering dietary GI, with minimal reduction to carbohydrate (compensated by slightly higher protein) content [29]. Thus, healthy low-GI/GL diets are essentially matched for calories, macronutrient distribution and other aspects of nutritional adequacy afforded by conventional healthy diets. The difference remains in the source of carbohydrates, primarily with respect to staples.

Possible Benefits of Low Glycaemic Index Diets in GDM Management

The advocacy for low-GI foods in promoting health draws from its ability to lower postprandial glycaemic and insulinaemic responses [17]. Chronic consumption of high-GI foods results in marked rise in glycaemia [17], and demands more insulin. This demand is initially compensated by increased insulin secretion [12]. This increased insulin demand exacerbates insulin resistance [12]. Hyperinsulinaemia and insulin resistance that are central to GDM pregnancies [2], eventually lead to β-cell fatigue and increased cardiovascular risks [12] as shown in Fig. 19.3.

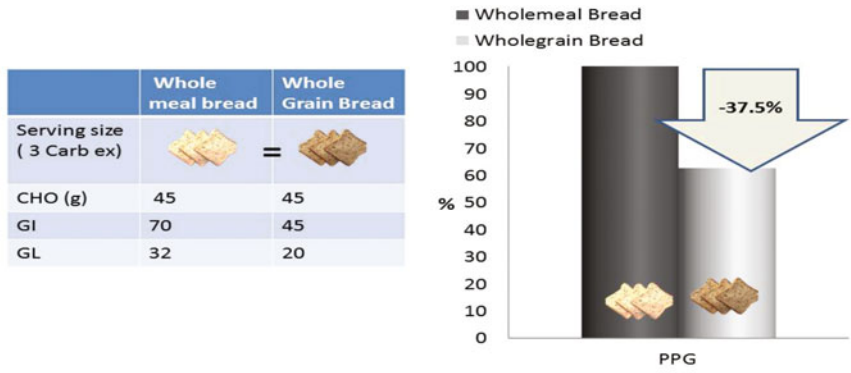
Table 19.1 Dietary recommendations use to lower dietary GI without causing major macronutrient changes

Food	Low-GI	Moderate-GI	High-GI
Recommendation	Encouraged	Moderation advised	Discouraged
Cereals and grains			
Rice	Parboiled	Basmati rice, brown rice, white rice with yoghurt (curd rice)	White rice, fragrant rice, Jasmine rice, glutinous rice
Bread	Multi-grain bread	Pita bread, chapatti made from wheat atta with dhal	White bread, wholemeal bread
Breakfast cereal	Muesli, coarse oat bran	Quick cooking/instant oats	Cornflakes, chocolate coated cornflakes, sugar coated cornflakes
Noodle and pasta	Macaroni, fettuccini spaghetti, noodles (al-dente)	Udon noodles plain	Rice noodles (fried)
Biscuits	Cream crackers—high calcium	Digestive biscuits, wholemeal biscuits, oatmeal biscuits	Wafers, sugar coated biscuits
Vegetables	Green peas, carrot, green vegetables	Sweet corn, sweet potato, yam	Pumpkin, tapioca potato
Fruits	Apple, orange, pear, plum, strawberry, dates	Grapes, banana, papaya, mango, raisins, pineapple	Watermelon, lychee
Legumes and nuts	Baked beans, kidney beans, soya beans, chick peas, lentils (dhal), mung beans, dried peas Nuts—though low in GI, moderation is encouraged	–	–
Dairy products	Skim milk, low-fat milk, low-fat yoghurt	Condensed sweetened milk	–

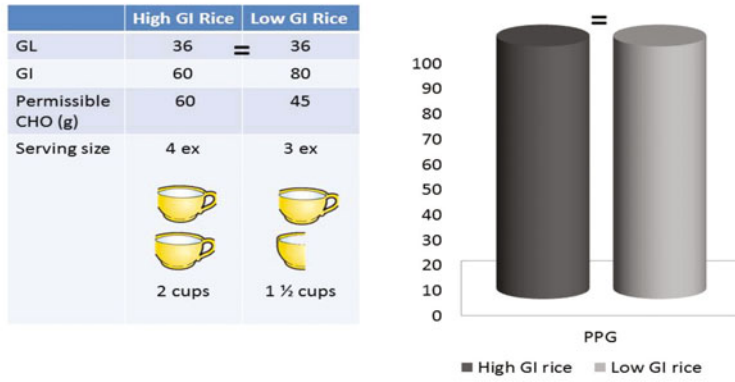
Source Adapted from Shyam et al. [86]
Note Serving size recommendations need to be adhered to even when using low-GI options
Legend GI: glycaemic index

In contrast, when compared with high-GI diets, low-GI diets show a slower and more sustained glycaemic response [30]. They prevent exaggerated postprandial glycaemic excursions during pregnancy [31]. Additionally, low-GI meals diminish glycaemic response to the subsequent meal [32]. Besides improving glycaemic control [33], low-GI diets improve insulin sensitivity [34] and increase β-cell function in individuals with impaired glucose tolerance [35, 36] and T2DM [37]. These actions prevent the degeneration of the glucose tolerance [16] and suggest the potential benefit of low-GI diet in GDM management.

Low-GI foods also lead to the increased secretion of anorexic gut hormones which induce satiety and suppress appetite [39, 40]. Therefore voluntary energy intake is reduced for the rest of the day after a low-GI meal is consumed [41]. Moreover, low-GI diets prevent decreases in fat oxidation induced by hyperglycaemia and hyperinsulinaemia; and increases lipolysis [38, 42]. The postulated mechanisms of action of dietary GI in modulating fat oxidation and body weight gain [42–47] are compiled in Fig. 19.4. Furthermore, low-GI diets increase protein retention in both normal and hyperinsulinaemic men [48] and favour lean body mass retention [38]. Whether these mechanisms can further optimise body weight management in GDM women, who are more likely to be obese and gain more weight during and after pregnancy [1], remains to be established.



Comparison of the postprandial glycaemic responses of breads varying in GI, when the portion size is maintained constant



Comparison of the potential serving size of rice varying in GI to maintain a constant GL

Fig. 19.2 Postulated practical application of GL concept. *Legend* GI: glycaemic index, GL: glycaemic load, CHO: carbohydrate amount (g), PPG: postprandial glycaemic response. *Top panel* shows that a similar portion of a lower GI option (wholegrain bread) versus a higher GI option (wholemeal bread) will reduce GL and hence result in lower postprandial glycaemic response. *Bottom panel* shows that theoretically a smaller serving size of a higher GI option (high-GI rice: e.g. glutinous rice) can have a similar GL as a slightly larger serving size of a lower GI option (low-GI rice: e.g. Basmati rice). However the increase in total calories as the number of carbohydrate exchange increases should be considered

Additionally, low-GI diets by virtue of increased production of short chain fatty acids (SCFA) from colonic fermentation [49], decrease the colonic luminal pH and stimulate the absorption of minerals such as calcium, potassium, magnesium, copper, zinc and selenium [50]. Colonic fermentation also increases folate availability and promotes normal homocysteine concentrations [16, 51]. Colonic fermentation moreover reduces inflammation by altering the bacterial species in the colon [52]. These effects of low-GI diets need to be verified in GDM women.

Table 19.2 Comparing options to lower dietary GL of a sample 1800 kcal diet

	Sample		Option A		Option B	
Diet	Standard healthy diet		Low-GI diet option		Low-carbohydrate diet option	
	g	% en	g	%en	g	% en
Carbohydrate	248	55	248	55	**180**	**40**
Protein	90	20	90	20	**68**	**15**
Fat	50	25	50	25	**70**	**35**
Diet GI	65		**50**		65	
Estimated diet GL	160		124		120	
Satisfies dietary guidelines	Yes		Yes		No	
Diet GI classification	Medium		Low		Medium	
Expected magnitude of dietary change	None		Medium		High	

Legend GI: glycaemic index, GL: glycaemic load
Bolded portions in Columns "Option A and B" highlight the changes made to the sample healthy diet to lower dietary GL. To achieve a similar reduction in dietary GL, the low-carbohydrate option increases fat intake and requires the implementation of drastic dietary changes

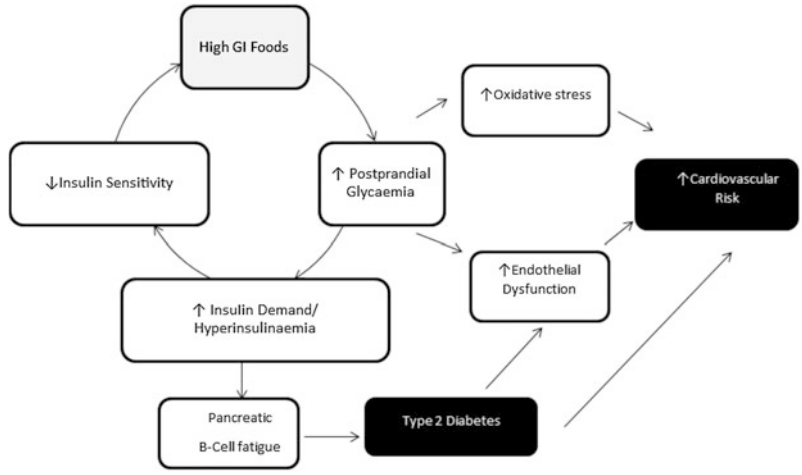


Fig. 19.3 Potential mechanisms of low-GI diets in the management of glucose homeostasis and cardiovascular risks. Legend: ↑: increase; ↓: decrease, *GI* glycaemic index

Interestingly, low-GI diets are especially beneficial to those with central obesity, insulin resistance, hyperinsulinaemia, diabetes, hypertension and metabolic syndrome [24, 53–56]. In such populations, low-GI/GL diet favours weight reduction, glycaemic control and CVD risk reduction, suggesting its potential success in the management of GDM, a condition that shares many of these risks.

In light of the pathophysiological similarities between GDM and T2DM [4], it is pertinent to note that data adds moderate to strong support for the use of low-GI diets in diabetes management [57–60]. American Diabetes Association grades the evidence to support the substitution of high-GL foods with those with lower GL, to modestly improve glycaemic control in diabetes at "level C" [61].

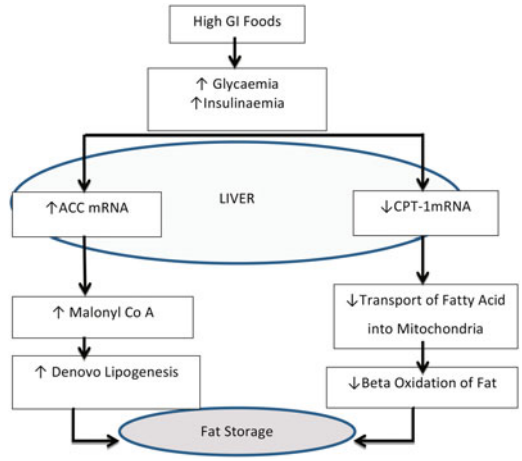


Fig. 19.4 GI and fat oxidation. Legend: ↑: increase; ↓: decrease, *GI* glycaemic index. High-GI foods reduce hepatic carnitine palmitoyltransferase-1(CPT-1) messenger RNA (mRNA) expression [42]. CPT-1 transport fatty acids into mitochondria for oxidation. High-GI foods concomitantly increase hepatic acetyl-CoA carboxylase (ACC) mRNA expression. ACC catalyses the formation of malonyl-CoA. Malonyl-CoA is a potent inhibitor of CPT-1, resulting in decreased fatty acid oxidation [42, 43]. Thus, high-GI foods lower lipolysis and facilitate fat storage

Current Evidence for the Role of Low Glycaemic Index and Glycaemic Load Diets in GDM Management

For Maintaining or Achieving Glycaemic Control During Pregnancy

Limited evidence supports the effectiveness of low-GI diet in maintaining a good glycaemic control in GDM pregnancies. Only three recent RCTs have investigated the impact of low-GI diet on blood glucose-related parameters [62–64].

Moses et al.'s intervention on women with GDM ($n = 63$) at 28 weeks of gestation, found only 29% ($n = 9$) of women receiving low-GI diets required insulin, as compared to 59% ($n = 19$) of women on a conventional-high-fibre-higher-GI-diet [62]. Eventually, 50% ($n = 9$) of these 19 women avoided insulin use after changing to a low-GI diet. However, the final GI of women in both groups were statistically similar and it was noted that increased fibre intake, reduction in carbohydrate intake and self-restriction of energy which occurred in both groups may have interfered with the study outcomes.

Grant and colleagues reported a pilot study ($n = 47$) on the feasibility and effectiveness of a low-GI diet on glycaemic control of GDM women [63]. In contrast to Moses et al. [62], Grant et al. reported lower dietary GI in the low-GI vs. the control group (49 vs. 58, $p = 0.001$). Improvements in glycaemic control in both groups were reported, but 58% of low-GI group had postprandial glucose within target as compared to 49% of control group ($p < 0.001$). This study was not powered to detect the small difference in self-monitored blood glucose (0.1–0.2 mmol/L) and postprandial blood glucose (1.2 mmol/L) observed between the study groups.

The most recent study by Hu et al. [64] was a relatively short 5-day intervention that compared the effectiveness of a low-GI staple versus a normal diabetic control diet among GDM women ($n = 140$) in Guangdong, China. Similar to the earlier studies, postprandial glucose levels were significantly reduced in both groups. However, post-intervention glucose levels taken after each meal were significantly reduced only in the low-GI group. There were also significantly greater reductions in glucose values from baseline in low-GI compared to the control group. The researchers observed a reduction in

glucose parameters after breakfast in this group, though low-GI staple foods were only consumed at lunch and dinner. While the generalisability of the study findings may be limited to Asian women and the feasibility of adhering to a low-GI staple diet can be questioned due to a very short intervention period, the study nevertheless has set a good precedence for future exploration in this area.

Cumulatively these findings suggest that lowering the GI of standard diets by substituting high-GI staples with low-GI options may improve management of glycaemia in GDM women and reduce the likelihood of requiring insulin therapy. This interpretation is further supported by a meta-analysis [65] involving 257 participants that confirmed lesser use of insulin in the low-GI diet group (RR = 0.767, 95% CI = 0.597–0.986, p = 0.039) compared to those in control group. This translates into 13 out of 100 GDM women avoiding the use of insulin by adopting a low-GI diet during pregnancy [65].

Prevention of Complications in Pregnancy and Neonatal Outcomes

Foeto-placental overgrowth and higher infant body fat has been associated with high-GI intake during pregnancy, while low-GI diet reduces these tendencies [62, 66]. A small but intensive study by Moses and colleagues [62] showed that the consumption of low-GI diet in the second and third trimesters in normoglycaemic mothers reduced foetal birth weight, foetal percentile and Ponderal index. However PREGGIO, a similar but larger trial [67] found that an early intervention at 20 weeks of gestation did not result in significant differences in similar neonatal outcomes.

Accordingly, Louie et al. reported no significant difference in pregnancy outcomes such as birth weight, birth weight centile, prevalence of macrosomia, Ponderal index and adverse pregnancy outcomes after a low-GI dietary intervention that included a minimum of three face-to-face counselling sessions with a dietician [68]. The researchers postulated that a relative small five-point difference in GI between the study groups, early nutrition counselling for both groups, relatively lower GI than norm at the baseline, timing (third trimester) and short duration of the intervention (6–7 weeks) may have contributed to the findings. Another justification for the lack of difference may be the high proportion of participants with normal BMI (68%) and the researchers are now hypothesising low-GI diet to be more efficient among overweight and obese pregnant mothers who have higher level of insulin resistance and deficiency of β-cells [69]. However, it can be concluded that both low-GI and high fibre diet produce optimal pregnancy outcomes and this further strengthens the argument for safety of low-GI diet in the management of GDM.

The significant relationship between maternal glycaemic control and neonatal outcomes has been well-established [70–73]. Higher fasting glucose during initiation of diet therapy was associated with increased neonatal fat mass and elevated C-peptide among women treated for mild GDM in a multicentre RCT [71]. A higher prevalence of elevated C-peptide levels and neonatal outcomes such as macrosomia and large-for-gestational age babies were found among women with higher fasting blood glucose at the final two weeks of gestation. The findings were consistent with an earlier study which described fasting glucose levels to be associated with neonatal adiposity and increased skinfold thickness in neonates, regardless of whether maternal GDM was treated with diet or insulin [72]. Expectedly, secondary analysis of the ROLO study [70] found low-GI dietary intervention in pregnancy to have a beneficial effect on neonatal central adiposity, which was also positively associated with mother's postprandial glucose. Although the study was conducted among normoglycaemic pregnant women, modest reductions in GI and GL were sufficient to lower neonatal waist: length ratio in the intervention group. This indicates that improved dietary carbohydrate quality may be associated with reduced neonatal central adiposity rather than birth weight. More importantly, epidemiologic studies among healthy pregnant women have found associations between high diet GI and congenital malformations such as neural tube defects, musculoskeletal and gastrointestinal defects [74].

These findings illustrate the importance of carbohydrate quality during pregnancy to promote neonatal well-being. However, while available data indicates the potential role of low-GI diets in reducing fat mass and central adiposity in neonates born to GDM mothers, there is insufficient evidence to establish the benefit of low-GI diets in preventing excessive maternal weight gain, foetal abnormalities, pregnancy complications or adverse pregnancy outcomes.

Prevention of GDM Recurrence and Overt Development of Diabetes

There is limited evidence relating low-GI diets and recurrence of GDM or development of T2DM among women with prior GDM. A recent Asian study [75] among women with prior GDM, compared the effectiveness of low-GI diet and conventional healthy dietary recommendations and reported improvements in glucose tolerance with low-GI educational intervention. The greatest improvement in glucose tolerance was observed among women with higher baseline insulin levels and in the lowest quartile of dietary GI at six months. The researchers also noted a significant reduction in 2-h post-75 g-oral glucose tolerance test (2HPP). In contrast, 2HPP levels increased in the comparison group, resulting in a significant difference in 2HPP changes between groups (Mean difference = 2.4 mmol/L, $p = 0.004$). It was suggested that a reduction of 2HPP by more than 0.84 mmol/L may halve the risk for T2DM and low-GI diet may be able to deliver that especially among women with a history of GDM and higher insulin levels.

In another distinctive study by Ostman and colleagues [76], seven women with impaired glucose tolerance and history of GDM were provided with either low-GI/high-fibre or high-GI/low-fibre bread products, during two consecutive 3-week periods, separated by a three-week washout period. The women receiving low-GI/high fibre bread had 35% lower insulin response to intravenous glucose challenge, though no effect was found on fasting glucose, insulin or lipid markers within the short 3 weeks of intervention. However, the sustainability of the effect remains to be established.

Concerns with the Use of Low-GI Diets

Since its inception, the utility of GI concept has been voraciously debated citing methodological issues and nutritional concerns [18].

Methodological Issues

Among the technical objections, the applicability of GI in mixed meals is predominantly questioned. However, studies reporting a lack of association between GI and glycaemic response when foods are taken as part of a mixed meal [77, 78] are thought to be methodologically flawed [14]. When analysed using standardised methods, the relative glycaemic impact of mixed meals is reportedly predicted by the amount of available carbohydrate they contain and the GI of their components [14].

The practical applicability of GI concept is also limited by the lack of a comprehensive GI database [24, 27]. While the international listing of GI and GL values is indeed comprehensive [13], determination of GI values of local foods is a work in progress in many countries. GI determination is cost and labour intensive and simplified methods have been devised to appropriately match foods and assign GI values to those with unknown values, till more local GI values become available [79]. As many factors affect the GI of a food, including its species, maturity (ripeness), storage time,

processing and cooking method, [27], technical uncertainties exist in this estimation process. Estimation of diet GI and GL require in-depth knowledge of carbohydrate intake [16] and food composition tables lack the intricate detail necessary to accurately match foods and their glycaemic response [80]. However, this limitation affects not only the reliability of estimating dietary GI but of all other nutrients as well. Specific biomarkers to assess diet intake, including diet GI, need to be established and will improve the objectivity of dietary assessments.

The relationship between the dietary fibre content and the GI of a food despite being modest [81], confounds existing evidence for the health impact of low-GI diets which are also consistently higher in dietary fibre [27]. While the proponents of GI point to validity and reproducibility of GI values determined in standardised laboratories [29], phenotypic differences among populations in response to starch exist [82] and may limit the application of GI values as it is currently determined.

Nutritional Concerns

Nutritional concerns in using GI stem from the fear that it may incite public to consume foods low in GI but high in fat and sugars like ice-cream, cookies, etc. [18, 27, 83]. However, GI proponents argue that GI should be applied only to low-fat starchy foods [84]. GI was never meant to be used in "isolation", but as an adjunct to other healthy eating principles [27]. Therefore the GI concept cannot replace, but should rather supplement existing nutritional strategies [18]. Perhaps the best approach to include GI education in diabetes counselling is to focus on individualisation [83] and this requires appropriate dietetic supervision.

Practical Issues with Implementation

The complexity of the GI/GL concepts make it difficult for patients to comprehend and implement the recommendations [18, 83, 85]. However, many low-GI diet books for weight control and wellness have been well-received in the West. Whether this acceptance can be extended to the other parts of the globe remains to be answered. Interestingly, various efforts at developing simplified GI-education modules have been successful. Categorising carbohydrates with simple terms like "gushers" and "tricklers" may ease patient comprehension of the concept [17]. Asian RCTs have shown that adults can be counselled to follow low-GI diets without having to memorise GI values [24, 86]. However, these are findings from clinical trials run by trained researchers and the practicality of providing GI-education in conventional healthcare settings remains to be proven.

Another concern with low-GI diets is that it can limit food choices and compromise nutritional adequacy [18, 83]. This may be especially important when dealing with pregnant women. Although traditional Indian and Greek cuisines include more low-GI foods than typical Western diets [83], adopting these food patterns may not be practical for all. Furthermore, food industries face challenges in producing palatable low-GI foods [84]. The issue is further compounded by the absence of a universally accepted logo that would facilitate consumer recognition of low-GI products.

While trials lasting a year or more show similar rates of adherence to low-GI and standard diets across continents [37, 87, 88], feasibility of long-term adherence to low-GI diets is unknown. While it may be possible to plan low-GI diets economically [86], its cost-effectiveness also remains to be established.

Recommendations

While emerging evidence suggests the possible benefit of low-GI diets in GDM management, there is urgent need for validation of the results. Optimising caloric intake to individual needs, restricting saturated fat, and distributing carbohydrates throughout the day will aid management of body weight and prevent of the degeneration of glucose tolerance in GDM women. Dietary recommendations should continue to encourage a moderate carbohydrate diet (45–50%), with adequate dietary fibre (25–30 g). Accordingly, dietary recommendations should encourage the inclusion of whole grains, beans, rolled oats, low-fat dairy and lean meat products, while being mindful of the daily energy needs. These strategies while in-line with conventional dietary goals, will also lower diet GI. Switching to low-GI-staples (such as whole grain breads, low-GI rice varieties and pasta) can be encouraged, taking cues from individual preferences. While adopting low-GI diets, there is a need to continue monitoring the portion sizes since postprandial glycaemia is affected by both the quantity and quality of carbohydrates. Low-GI diets that satisfy other nutritional considerations are acceptable in the treatment of GDM.

Conclusions

Existing evidence suggests that lowering the GI of conventional healthy diets may be beneficial in GDM treatment for managing maternal glycaemia and neonatal adiposity. However, a few practical issues in implementing low-GI dietary recommendations remain unresolved at present. There is an urgent need for adequately powered, well-controlled trials to further investigate the feasibility, acceptability, adherence, safety, clinical and cost effectiveness of low-GI dietary recommendations in GDM management.

Acknowledgements The authors acknowledge Prof. Dr. Winnie Chee, International Medical University, KL for her guidance while preparing the manuscript.

References

1. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diab Care. 2007;30(Suppl. 2):S251–S60.
2. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diab Care. 2007;30(Suppl. 2):S112–9.
3. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, et al. Glycemic index, glycemic load, and chronic disease risks-a meta-analysis of observational studies. Am J Clin Nutr. 2008;87(3):627–37.
4. Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA. 1997;278(13):1078–83.
5. Butte FN. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000;71(suppl):1256S–61S.
6. Moses RG, Cefalu WT. Considerations in the management of gestational diabetes Mellitus: “You Are What Your Mother Ate!”. Diabetes Care. 2016;39:13–5.
7. Hernandez TL, Anderson MA, Chartier-Logan C, Friedman JE, Barbour LA. Strategies in the nutritional management of gestational diabetes. Clin Obstet Gynecol. 2013;56(4):803–15.
8. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002;76:5–56.

9. Cypryk K, Kaminska P, Kosinski M, Pertynska-Marczewska M, Lewinski A. A comparison of the effectiveness, tolerability and safety of high and low carbohydrate diets in women with gestational diabetes. Endokrynol Pol. 2007;58(4):314–9.
10. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. New Engl J Med. 2001;345(11):790–7.
11. Different types of dietary advice for women with gestational diabetes mellitus (Review) [Internet]. Wiley; 2013.
12. Augustin LSFS, Jenkins DJ, Kendall CW, La Vecchia C. Glycemic index in chronic disease: a review. Eur J Clin Nutr. 2001;56:1049–71.
13. GI database [Internet]. 2012. Available from http://www.glycemicindex.com.
14. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in Glycemic Index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. Am J Clin Nutr. 2006;83:1306–12.
15. Jenkins D, Wolever T, Taylor R, Barker H, Fielden H, Baldwin J, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34(3):362–6.
16. Wolever TMS. The glycaemic index: a physiological classification of dietary carbohydrate. Oxfordshire, UK: CABI Publishing; 2006 227 p.
17. Burani J. Gushers and Tricklers: Practical use of the glycemic index [Powerpoint Presentation]. Marco Island, Florida: University of Sydney; 2006 [cited 2010 11 March]. Available from http://www.glycemicindex.com/glycemic.index.ppt.
18. Kalergis M. The role of the glycemic index in the prevention and management of diabetes: a review and discussion. Can J Diab. 2005;29:27–38.
19. Jenkins DJJA, Wolever TM, Collier GR, Rao AV, Thompson LU. Starchy foods and fiber: reduced rate of digestion and improved carbohydrate metabolism. Scand J Gastroenterol Suppl. 1987;129:132–41.
20. Yoon J, Thompson L, Jenkins D. The effect of phytic acid on in vitro rate of starch digestibility and blood glucose response. Am J Clin Nutr. 1983;38(6):835–42.
21. Johnston CS, Stelewska I, Long CA, Harris LN, Ryals RH. Examination of antiglycemic properties of vinegar in healthy dults. Ann Nutr Metab. 2010;56(1):74–9.
22. Holm J, Lundquist I, Bjorck I, Eliasson A, Asp N. Degree of starch gelatinization, digestion rate of starch in vitro, and metabolic response in rats. Am J Clin Nutr. 1988;47(6):1010–6.
23. Chew I, Brand J, Thorburn A, Truswell A. Application of glycemic index to mixed meals. Am J Clin Nutr. 1988;47:53–6.
24. Yusof BNM. A randomized control trial of low glycemic index against conventional carbohydrate exchange diet on glycemic control and metabolic parameters in type 2 diabetes [Thesis]. Kuala Lumpur: Universiti Kebangsaan Malaysia; 2008.
25. Goff LM, Frost GS, Hamilton G, Thomas EL, Dhillo WS, Dornhorst A, et al. Carbohydrate-induced manipulation of insulin sensitivity independently of intramyocellular lipids. Br J Nutr. 2003;89(03):365–74.
26. Amano Y, Sugiyama M, Lee JS, Kawakubo K, Mori K, Tang AC, et al. Glycemic index-based nutritional education improves blood glucose control in Japanese adults: a randomized controlled trial. Diab Care. 2007;30(7):1874–6.
27. Miller J. The glycaemic index of foods. Asia Pacific J Clin Nutr. 1993;2:107–10.
28. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA. 1997;277(6):472–7.
29. Augustin LSA, Kendall CWC, Jenkins DJA, Willett WC, Astrup A, Barclay AW, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). Nutr Metab Cardiovasc Dis. 25(9):795–815.
30. Wolever TM. The glycemic index. World Rev Nutr Diet. 1990;62:120–85.
31. Louie JCY, Brand-Miller JC, Markovic TP, Ross GP, Moses RG. Glycemic index and pregnancy: a systematic literature review. J Nutr Metab. 2011;2010.
32. Brighenti F, Benini L, Del Rio D, Casiraghi C, Pellegrini N, Scazzina F, et al. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. Am J Clin Nutr. 2006;83(4):817–22.
33. Jenkins DA, Kendall CC, McKeown-Eyssen G, et al. Effect of a low–glycemic index or a high–cereal fiber diet on type 2 diabetes: a randomized trial. JAMA. 2008;300(23):2742–53.
34. Barr S, Reeves S, Sharp K, Jeanes YM. An isocaloric low glycemic index diet improves insulin sensitivity in women with polycystic ovary syndrome. J Acad Nutr Diet. 2013;113(11):1523–31.
35. Wolever TMS, Mehling C. High-carbohydrate low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance. Br J Nutr. 2002;87(5):477–87.
36. Laaksonen DE, Toppinen LK, Juntunen KS, Autio K, Liukkonen K-H, Poutanen KS, et al. Dietary carbohydrate modification enhances insulin secretion in persons with the metabolic syndrome. Am J Clin Nutr. 2005;82(6):1218–27.

37. Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87(1): 114–25.
38. Brand-Miller JC, Holt SH, Pawlak DB, McMillan J. Glycemic index and obesity. Am J Clin Nutr. 2002;76 (1):281S–5S.
39. Lavin J, Wittert G, Andrews J, Yeap B, Wishart J, Morris H, et al. Interaction of insulin, glucagon-like peptide 1, gastric inhibitory polypeptide, and appetite in response to intraduodenal carbohydrate. Am J Clin Nutr. 1998; 68(3):591–8.
40. Holt S, Brand J, Soveny C, Hansky J. Relationship of satiety to postprandial glycaemic, insulin and cholecystokinin responses. Appetite. 1992;18(2):129–41.
41. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics. 1999;103:e26.
42. Wolfe R. Metabolic interactions between glucose and fatty acids in humans. Am J Clin Nutr. 1998;67(3): 519S–26S.
43. Pawlak D, Denyer GS, Brand-Miller JC. Long term feeding with high glycemic index starch leads to obesity in mature rats. Proc Nutr Soc Aust. 2000;24:215 (abstract).
44. Zurlo F, Lillioja S, Esposito-Del Puente A, Nyomba BL, Raz I, Saad MF, et al. Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. Am J Physiol Endocrinol Metab. 1990;259(5):E650–7.
45. Simoneau J-A, Veerkamp JH, Turcotte LP, Kelley DE. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. FASEB J. 1999;13(14):2051–60.
46. Febbraio MA, Keenan J, Angus DJ, Campbell SE, Garnham AP. Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: effect of the glycemic index. J Appl Physiol. 2000;89(5):1845–51.
47. Kiens B, Richter E. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. Am J Clin Nutr. 1996;63(1):47–53.
48. Howe JC, Rumpler WV, KM. B. Dietary starch composition and level of energy intake alter nutrient oxidation in 'carbohydrate-sensitive' men. J Nutr. 1996;126:2120–9.
49. FAO/WHO. Carbohydrates in Human nutrition: report of a joint FAO/WHO expert consultation. In: FAO/WHO, editor. Rome 14–18 April 1997.
50. Metzler-Zebeli BU, Hooda S, Mosenthin R, Ganzle MG, Zijlstra RT. Bacterial fermentation affects net mineral flux in the large intestine of pigs fed diets with viscous and fermentable nonstarch polysaccharides. J Anim Sci. 88(10):3351–62.
51. Houghton L, Green T, Donovan U, Gibson R, Stephen A, O'Connor D. Association between dietary fiber intake and the folate status of a group of female adolescents. Am J Clin Nutr. 1997;66(6):1414–21.
52. Neish AS, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V, et al. Prokaryotic regulation of epithelial responses by inhibition of IκB-α ubiquitination. Science. 2000;289(5484):1560–3.
53. Frost G, Wilding J, Beecham J. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 diabetic patients. Diab Med. 1994;11(4):397–401.
54. Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. Am J Clin Nutr. 2005;81 (5):976–82.
55. Frost GS, Brynes AE, Bovill-Taylor C, Dornhorst A. A prospective randomised trial to determine the efficacy of a low glycaemic index diet given in addition to healthy eating and weight loss advice in patients with coronary heart disease. Eur J Clin Nutr. 2004;58(1):121–7.
56. Ghani RA, Shyam S, Arshad F, Wahab NA, Chinna K, Safii NS, et al. The influence of fasting insulin level in post-gestational diabetes mellitus women receiving low-glycaemic-index diets. Nutr Diabetes. 2014;4:e107.
57. Wheeler ML, Dunbar SA, Jaacks LM, Karmally W, Mayer-Davis EJ, Wylie-Rosett J, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. Diab Care. 2012;35(2):434–45.
58. Rivellese AA, Giacco R, Costabile G. Dietary carbohydrates for diabetics. Curr Atherosclerosis Rep. 2012; 14(6):563–9.
59. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr. 2013;97(3):505–16.
60. Mann JI, Te Morenga L. Diet and diabetes revisited, yet again. Am J Clin Nutr. 2013;97(3):453–4.
61. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diab Care. 2013;36(11):3821–42.
62. Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial. Diab Care. 2009;32(6):996–1000.
63. Grant SM, Wolever TMS, O'Connor DL, Nisenbaum R, Josse RG. Effect of a low glycaemic index diet on blood glucose in women with gestational hyperglycaemia. Diab Res Clin Pract. 2011;91(1):15–22.

64. Hu Z-G, Tan R-S, Jin D, Li W, Zhou X-Y. A low glycemic index staple diet reduces postprandial glucose values in Asian women with gestational diabetes mellitus. J Investig Med. 2014;62(8):975–9.
65. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. Diab Care. 2014; 37(12):3345–55.
66. Moses RG, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, et al. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 2006;84(4):807–12.
67. Moses RG, Casey SA, Quinn EG, Cleary JM, Tapsell LC, Milosavljevic M, et al. Pregnancy and glycemic index outcomes study: effects of low glycemic index compared with conventional dietary advice on selected pregnancy outcomes. Am J Clin Nutr. 2014;99(3):517–23.
68. Louie JCY, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, et al. A randomized controlled trial investigating the effects of a low–glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. Diab Care. 2011;34(11):2341–6.
69. Catalano P, Vargo K, Bernstein I, Amini S. Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. Am J Obstet Gynecol. 1991;165:914–9.
70. Horan MK, McGowan CA, Gibney ER, Donnelly JM, McAuliffe FM. Maternal low glycaemic index diet, fat intake and postprandial glucose influences neonatal adiposity–secondary analysis from the ROLO study. Nutr J. 2014;13(1):1.
71. Durnwald CP, Mele L, Spong CY, Ramin SM, Varner MW, Rouse DJ, et al. Glycemic characteristics and neonatal outcomes of women treated for mild gestational diabetes. Obstet Gynecol. 2011;117(4):819.
72. Uvena-Celebrezze J, Fung C, Thomas A, Hoty A, Huston-Presley L, Amini S, et al. Relationship of neonatal body composition to maternal glucose control in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2002;12(6):396–401.
73. Pedersen J. Diabetes and pregnancy; blood sugar of newborn infants during fasting and glucose administration. Ugeskrift laeger. 1952;114(21):685.
74. Parker SE, Werler MM, Shaw GM, Anderka M, Yazdy MM. Dietary glycemic index and the risk of birth defects. Am J Epidemiol. 2012;176(12):1110–20.
75. Shyam S, Arshad F, Ghani RA, Wahab NA, Safii N, Nisak MY, et al. Low glycaemic index diets improve glucose tolerance and body weight in women with previous history of gestational diabetes: a six months randomized trial. Nutr J. 2013;12(1):1.
76. Östman E, Frid A, Groop L, Björck I. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. Eur J Clin Nutr. 2006;60(3):334–41.
77. Hollenbeck CBCA, Reaven GM. Comparison of plasma glucose and insulin responses to mixed meals of high, intermediate- and low-glycemic potential. Diab Care. 1988;11:323–9.
78. Laine DCTW, Levitt MD, Bantle JP. Comparison of predictive capabilities of diabetic exchange lists and glycemic index of foods. Diab Care. 1987;10(4):387–94.
79. Louie JC-Y, Flood V, Turner N, Everingham C, Gwynn J. Methodology for adding glycemic index values to 24-hour recalls. Nutrition. 2010;30:1–6.
80. Wolever T, Jenkins D, Jenkins A, Josse R. The glycemic index: methodology and clinical implications. Am J Clin Nutr. 1991;54(5):846–54.
81. Wolever T. Relationship between dietary fiber content and composition in foods and the glycemic index. Am J Clin Nutr. 1990;51(1):72–5.
82. Mandel AL, Breslin PAS. High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. J Nutr. 2012;142(5):853–8.
83. Palmer S. Finding a place for the glycemic index. Today's Dietitian [Internet]. 2009;11(6):8 p. Available from http://www.todaysdietitian.com/newarchives/060109p8.shtml.
84. Brand-Miller J, Foster-Powell K, Nutr M. Diets with a low glycemic index: from theory to practice. Nutr Today. 1999;34(2):64–72.
85. Beebe C. Diets with a low glycemic index: not ready for practice yet!! Nutr Today. 1999;34(2):82–6.
86. Sangeetha-Shyam, Fatimah A, Rohana AG, Norasyikin AW, Karuthan C, Nik Shanita S, et al. Lowering dietary glycaemic index through nutrition education among Malaysian women with a history of gestational diabetes mellitus. Mal J Nut. 2013;19(1):9–23.
87. Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. Am J Clin Nutr. 2007;86(3):707–13.
88. Shyam S, Arshad F, Ghani RA, Wahab NA, S. NS, Chinna K, et al. Effect of including glycaemic index (GI) nutrition education, within the conventional healthy dietary recommendation framework, on body weight and composition of women with prior gestational diabetes mellitus: results from a one-year randomised controlled trial. Mal J Nutr. 2015;21(3):269–83.

Chapter 20
Low-Carbohydrate Diet for the Treatment of Gestational Diabetes Mellitus

Cristina Moreno-Castilla, Marta Hernandez and Dídac Mauricio

Key Points

- CHO are the main macronutrients influencing postprandial glucose levels, and thus, diets for GDM usually manipulate the amount, quality or distribution of CHO.
- A minimum daily intake of 175 g CHO for pregnant women is recommended, regardless of whether GDM is present; however, there is no consensus on the optimal amount of CHO in women with GDM.
- Although there is not enough evidence concerning a potential negative impact of mild ketosis on the foetus, ketonuria or ketonaemia are commonly monitored in pregnant women with GDM treated with low-CHO diets.
- By definition, in non-pregnant adults, low-CHO diets contain <130 grams of CHO per day or <26% of total daily energy; however, for the purpose of this review, a low-CHO diet in GDM is a diet with the lowest CHO content used in a given trial (usually between 35 and 45% of total energy).
- Although low-CHO diets for GDM are safe and, in some cases, have been more beneficial to pregnancy outcomes than higher CHO diets, there is not enough evidence favouring this choice over others as MNT for GDM.
- There are few clinical trials addressing the overall dietary CHO content.
- Practice guidelines for GDM tend to recommend low-CHO diets, despite the sparse evidence.

Keywords Carbohydrates · Diet · Gestational diabetes · Gestational diabetes mellitus · Medical nutrition therapy · Nutrition therapy

Abbreviations

ADA American Diabetes Association
AUC Area under the curve

C. Moreno-Castilla
Department of Endocrinology and Nutrition, Hospital Universitari Arnau de Vilanova, Rovira Roure, 80, 25198 Lleida, Spain
e-mail: cristinamorenocastilla@gmail.com

M. Hernandez
Department of Endocrinology and Nutrition, Institut de Recerca Biomèdica de Lleida (IRBLleida), Hospital Universitari Arnau de Vilanova, Rovira Roure, 80, 25198 Lleida, Spain
e-mail: martahernandezg@gmail.com

D. Mauricio (✉)
Department of Endocrinology and Nutrition, CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Hospital Universitari Germans Trias I Pujol, Carretera de Canyet S/N, 08916 Badalona, Spain
e-mail: didacmauricio@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_20

CHO	Carbohydrate/s
CI	Confidence interval
GDM	Gestational diabetes mellitus
GI	Glycaemic index
GL	Glycaemic load
MNT	Medical nutrition therapy
RCT(s)	Randomized controlled trial (trials, in plural)
RR	Relative risk

Introduction

The digestion and subsequent absorption of carbohydrates (CHO) cause a rise in blood glucose; thus, postprandial glycaemia is CHO-dependent. This phenomenon has also been confirmed for pregnant women with gestational diabetes mellitus (GDM) [1]. In GDM, glucose intolerance is induced by maternal insulin resistance, resulting in maternal hyperglycaemia, which leads to foetal hyperinsulinism because of increased substrate delivery to the foetus. This pathological state can have negative maternal and infant consequences during and beyond pregnancy. Regarding the newborn, GDM is associated with shoulder dystocia, bone fracture, nerve palsy, deaths [2], excessive foetal growth reaching macrosomia [2–4], neonatal hyperglycaemia [3, 4] erythrocytosis, hyperbilirubinemia and stillbirths [4]. With respect to mothers, there is a higher rate of preeclampsia, caesarean delivery and postpartum depression [2]. Further, pregnant women with GDM have a higher risk of impaired glucose tolerance, type 2 diabetes and cardiovascular disease later in life, and their offspring also have a higher risk of type 2 diabetes [5] and obesity [6].

The main objective of GDM treatment is to avoid all GDM-associated complications through optimal glycaemic control, i.e. achieving normoglycaemia, while preventing ketosis and covering the nutritional requirements of the mother and foetus [7]. These targets can usually be achieved with diet only for the majority of women with GDM (52–92%) [8, 9]. For this reason, medical nutrition therapy (MNT), accompanied by physical activity, is the first-line treatment for GDM. The control of CHO is the mainstay of dietary treatment. Research into GDM diets has primarily been centred on this macronutrient; however, there are still little available data. Because pregnant women with GDM have the same nutritional needs as non-diabetic pregnant women, the recommended dietary CHO intake is a minimum of 175 g per day [10].

Different Approaches to Control Carbohydrates

The traditional approach consists of regulating the total amount, specifically by reducing intake. In type 1 and type 2 diabetes mellitus, it is well documented that restricting CHO produces immediate therapeutic benefits (reduction or elimination of medication in type 2 diabetes and lower insulin requirements in type 1 diabetes, among others) with a good adherence and no adverse effects comparable to the effects of pharmacological treatment [11].

Another approach is founded on the modification of the dietary glycaemic index (GI). First described in 1981 [12], the GI was used to estimate the in vivo blood glucose response to the intake of a given food item, relative to that of a CHO reference food. The GI has become the target of many studies, including clinical trials in GDM. However, another chapter in this book already presents an in-depth discussion of the use of low-GI diets for GDM treatment.

Later, the glycaemic load (GL) concept was introduced [13]. The GL comprises the quantity of CHO consumed and their GI. The GL is a better predictor of the postprandial glycaemia associated with a food or diet [14].

In this chapter, we will review the effects of low-CHO diets in GDM. The general hypothesis is that these strategies can achieve glycaemic goals in GDM and prevent the incidence of poor perinatal outcomes. Some authors have suggested that the total amount of CHO has a stronger contribution to the GL than GI [15]; however, there are no published randomized controlled trials (RCTs) comparing different GL diets in GDM.

An alternative method would be to distribute CHO into several meals and snacks in order to control postprandial glycaemia, but there are no trials addressing this issue [16].

Clinical Evidence of Low-Carbohydrate Diets for Gestational Diabetes Mellitus

– What do we mean when we say low carbohydrate?

One of the fears of reducing the CHO content is the induction of maternal ketosis, which may adversely affect the foetus. For this reason, ketonuria is usually measured in studies. Nevertheless, there is not enough evidence for the real negative impact of mild ketonaemia on the foetus.

Recently, the American Diabetic Association (ADA) Standards of Medical Care in Diabetes, due to a lack of sufficient evidence for the ideal macronutrient distribution for diabetes, recommended, with the lowest level of evidence, the individualization of dietary treatment to achieve energy and metabolic targets [17]. In the absence of a specific recommended percentage or amount of CHO for pregnant women with or without GDM, it is difficult to define low-CHO diets in normal physiological and pathological situations. A recent critical review suggested some definitions based on the dietary CHO content. Diets with a total of less than 130 grams of CHO per day or less than 26% of total energy in the form of CHO are proposed to be considered as low-CHO diets. Additionally, diets with a percentage of total energy from CHO between 26 and 45% would be considered moderately CHO-restricted diets, while high-CHO diets would provide more than 45% energy as CHO [11]. In this chapter, we will consider studies comparing any two dietary interventions with different CHO content, and the one with the lowest CHO amount will be considered the low-CHO diet because the classification proposed by the mentioned authors did not consider the particularities of pregnancy. It must be noted that 130 g/d of CHO is the minimum recommended for adults and children. For pregnant women, this value is higher, i.e. 175 g/d [10].

– Clinical trials with low-carbohydrate diets

Although modifying the quantity of CHO seems to be the first MNT approach for the treatment of GDM, there have been a few clinical trials comparing low-CHO with higher CHO diets. In all the diets tested in these trials, complex CHO prevail over simple sugars, but we will not expand on this matter because other chapter of this book addresses complex CHO diets for GDM. Table 20.1 summarizes the characteristics of the trials testing diets with different CHO content. We are, therefore, providing a detailed description of the few available studies.

In the early 1980s, Nolan et al. performed a small randomized crossover study comparing two diets. In one arm of the study, a low-CHO diet with 35% CHO (20% protein, 45% fat, 31 g fibre) was included. This was compared to a high-CHO diet, with 70% CHO (20% protein and 10% fat, 70 g fibre). Both diets were isocaloric and contained unrefined CHO. In both arms, the foods were provided by the investigators. Only five women participated in the study and adhered to each diet for a short period of 4 days. The researchers found that a low-CHO diet resulted in less favourable

Table 20.1 Clinical evidence of low-carbohydrate diets

Reference	Type of clinical trial	*N*	BMI	Ethnicity	Duration of intervention	Low-CHO diet % CHO (%)	High-CHO diet %CHO (%)	Main results of low-CHO diet
Nolan [18]	Randomized crossover	5	26.9 ± 8	NR	4 days each diet	35	70	Worse results in fasting plasma cholesterol ($P < 0.01$), FFA ($P < 0.02$) and glucose response to glucose load ($P < 0.05$) No differences in: plasma glucose, urinary glucose output, fasting plasma triglycerides and insulin response to glucose load
Major [19]	Non-randomized	42	NR	Hispanic	Until delivery	<42	45–50	Lower postprandial glucose values ($P < 0.04$), insulin need ($P < 0.048$), prevalence of births large for gestational age ($P < 0.035$), caesarean and macrosomia ($P < 0.037$) No differences but better HbA1c, no shoulder dystocia or birth trauma Ketonuria in two women
Cypryk [21]	Randomized	30	NR	Caucasian	14 days	45	Over 60	Low-CHO greater decrease glycemia after breakfast ($P < 0.05$) No difference in glucose fasting values, ketonuria or obstetric outcomes
Moreno-Castilla [22]	Randomized	152	26 ± 5	Caucasian	Until delivery	40	55	No differences in the rate of insulin or in pregnancy outcomes
Hernandez [24]	Randomized crossover	16	33.6 ± 1	Caucasian	12 days	40	60	Lower: postprandial glycemia, daytime mean glucose and lower AUC of postprandial glycemia and of 24 h total glucose values ($P = 0.02$) Higher FFA AUC
Hernandez [25]	Randomized crossover	12	Low-CHO: 33.4 ± 1.4 High CHO: 34.3 ± 1.6	Hispanic (high-CHO)/ Caucasian (low-CHO)	Until delivery	40	60	No benefits in terms of maternal insulin resistance and offspring adiposity

Abbreviations NR: not reported, FFA: free fatty acids, AUC: area under the curve

outcomes over high CHO with the following results: higher fasting plasma cholesterol (6.3 ± 1.1 mmol/L vs. 5.9 ± 1.1 mmol/L, $P < 0.01$), free fatty acids (FFA) (690 ± 270 µmol/L vs. 590 ± 270 µmol/L, $P < 0.02$) and glucose response to glucose load ($P < 0.05$). Nevertheless, there were no statistically significant differences in plasma glucose (fasting and postprandial), urinary glucose excretion, fasting plasma triglycerides or insulin response to a glucose load [18].

In 1998, Major et al. conducted a non-randomized non-controlled study of 42 women with gestational diabetes who were predominantly Hispanic. Participants were assigned to a low-CHO diet with less than 42% of total CHO content (25% protein, 35% fat) or a high content-CHO diet with 45–50% CHO. In a univariate analysis, the researchers found lower postprandial glucose values (110 ± 18 mg/dL versus 132 ± 19 mg/dL, $P < 0.04$) and daily insulin need (relative risk (RR) 0.14; 95% confidence interval (CI) 0.02, 1.0; $P < 0.048$) in the lower CHO group. The low-CHO diet also resulted in a larger reduction in HbA1c, although this finding was non-significant. Additionally, women in the low-CHO diet group had a lower frequency of large for gestational age newborns (RR 0.22; 95% CI 0.05, 0.091; $P < 0.035$), caesarean sections and macrosomia (RR 0.15; 95% CI 0.04, 0.94; $P < 0.037$). The only potential adverse effect of the low-CHO diet was the appearance of ketonuria in two women, which was managed by increasing the amount of CHO [19].

Conversely, in 2001, Romon et al. in a prospective observational nutrition survey sub-study developed in France, found that infant birth weight was negatively correlated with CHO intake (r −0.27, $P < 0.05$), a negative correlation that persisted after a forward-stepwise regression analysis [20].

In 2007, Cypryk et al. did not find any difference regarding fasting glucose values, ketonuria or obstetric outcomes in a randomized trial with 30 Caucasian women with GDM allocated to diets with either a 45% or 65% CHO content (25% protein and 30% fat or 25% protein and 15% fat, respectively), both with a total of 1800 kcal per day. Notwithstanding, only a low-CHO diet resulted in a significant reduction in postprandial breakfast glycaemia (102 ± 16 mg/dL before intervention vs 94 ± 11 mg/dL after intervention, $P < 0.021$) [21].

In 2007, the Fifth International Workshop Conference on GDM issued nutrition recommendations for women with GDM, including gestational weight gain, calorie intake, and macronutrient composition and distribution. These recommendations were based on the current limited available scientific evidence, while encouraging the performance of further controlled clinical trials comparing intensive dietary strategies, mainly focused on the amount, type and distribution of CHO [16]. Following these recommendations, our group designed and performed the first RCT comparing a low-CHO diet with 40% of the total energy content from CHO with a control diet with 55% of the total energy content from CHO. This trial was conducted in 152, mainly Caucasian, pregnant women with GDM [22]. The study hypothesis stated that a low-CHO diet would lead to less dietary treatment failure (main study outcome: the need for insulin treatment) with similar obstetric and perinatal outcomes. Both diets had a minimum of 1800 kcal per day. The protein content was 20% of the total calorie amount, and fat represented 40% in the low-CHO diet and 25% in the control diet. The difference in fat intake was achieved mainly by increasing the olive oil content. CHO were distributed into three main meals and three snacks, and these amounts and distribution were fixed unless the women reached the main study outcome (need of insulin treatment). The assessment of the CHO intake was made by estimated 3-day food records, and it reflected that the intake of total CHO was different between the groups, although most participants reported eating less CHO than prescribed (202.7 g/day and 177.1 g/day in the high and low-CHO groups, respectively, $P = 0.0001$). This difference in the CHO content was mainly due to an increase in the intake of starch in the high-CHO diet, as the intake of sugars was equivalent in both study groups. A total of 130 participants completed the trial, and the intention-to-treat analysis showed that there were no significant differences between both groups in the rate of insulin treatment (included insulin dose and time to insulin initiate) (54.7%) or in pregnancy outcomes.

It should be noted that when a lower CHO diet is prescribed to GDM patients, there should be a parallel increase in the percentage of fat to maintain the total energy supply, as the proportion of protein usually remains stable at 15–20% of total daily calories. Outside of pregnancy, it is well known that a high-fat diet increases serum FFA, promoting insulin resistance; this effect appears to be more deleterious for saturated fats [23]. Hernandez et al. [24] compared the glycaemic profiles and postprandial lipids of a conventional lower CHO/high-fat diet (40% CHO, 45% fat, 15% protein) versus the consumption of a higher complex CHO/lower fat CHOICE (Choosing Healthy Options in Carbohydrate Energy) diet (60% CHO, 25% fat, 15% protein). They designed a controlled randomized crossover trial, in which they provided two alternative regimens of 3-day diets to 16 pregnant women with overweight/obesity and GDM. The patients wore a continuous glucose monitor sensor (blinded), and, on the fourth day of each diet, they measured the postprandial (5 h) glucose, insulin, triglycerides and FFA after a breakfast meal test. Both diets comprised a minimum of 1800 kcal per day with the same distribution in each meal (three main meals and two snacks). Both diets provided similar amounts of fibre, serving foods with low-moderate GI, and simple sugars represented less than 30% of total CHO and less than 18% of total daily calories. The fatty acid content, mostly monounsaturated, was also similar. Women were blinded to the continuous glucose monitoring system values. The results showed that the low-CHO diet led to a lower overall 1 h postprandial glucose across three meals (107 ± 3 mg/dL vs. 115 ± 2 mg/dL, $P \leq 0.01$) and 2 h postprandial glucose across three meals (97 ± 3 mg/dL vs. 106 ± 3 mg/dL, $P = 0.001$). Specific, meal-related glycaemic profiles showed that a low-CHO diet led to a significantly lower 1 h postprandial glycaemia after lunch (101 ± 3 mg/dL vs. 115 ± 3 mg/dL, $P \leq 0.001$) and 2 h postprandial glycaemia after breakfast (99 ± 3 mg/dL vs. 111 ± 4 mg/dL, $P \leq 0.01$) and lunch (93 ± 3 mg/dL vs. 104 ± 3 mg/dL, $P \leq 0.001$). The mean daytime glucose was also lower in the low-CHO diet group (93 ± 3 mg/dL vs. 98 ± 2 mg/dL, $P = 0.03$), and the daytime glucose area under the curve (AUC) was also lower (93,663 ± 2630 mg·min/dL vs. 99,493 ± 2136 mg·min/dL, $P = 0.01$). The primary study outcome showed that the low-CHO diet resulted in lower 24-h total glucose values (128,653 ± 3810 mg·min/dL vs. 136,730 ± 2980 mg·min/dL, $P = 0.02$). Additionally, FFA were lower at the 5 h postprandial measurement of controlled breakfast test in the high-CHO diet, which led to a significantly lower FFA AUC. As higher FFA levels may induce excess foetal growth, the authors suggested that a diet liberalizing complex CHO and limiting fat (CHOICE) could be a strategy to prevent macrosomia.

After these results, these authors performed a pilot RCT comparing the effects of these two diets in terms of maternal insulin resistance, adipose tissue lipolysis and foetal adiposity in 12 overweight/obese pregnant women with GDM [25]. The low-CHO diet resulted in no benefits over the higher CHO diet. Furthermore, patients allocated to the CHOICE diet had a lower fasting glucose and FFA. An adipose tissue biopsy was performed, and studies showed greater insulin sensitivity and lower proinflammatory gene expression in those women that followed the CHOICE diet. The researchers also identified a trend towards lower infant adiposity from those pregnancies under the CHOICE diet, which was correlated with maternal fasting insulin and HOMA-IR. Finally, the authors attributed these effects to dietary fat.

Recommendations or Guidelines

In Table 20.2, we include a brief summary of the recommendations of the principal guidelines concerning MNT for GDM. Despite the poor evidence and the lack of benefit for low-CHO diets for GDM, most guidelines recommend a low intake of CHO during GDM (between 35 and 50% of total energy from CHO), always covering the DRI for pregnant women of 175 g of CHO per day [7, 27]. The American Academy of Nutrition and Dietetics [27] recommends that CHO should represent less

Table 20.2 Summary of more recent recommendations of different organizations about carbohydrates for gestational diabetes mellitus[b]

Organization	Year	CHO amount recommended
AND [27]	2008	DRI A minimum of 175 g/day <45%[a]
ADA [7]	2007	DRI A minimum of 175 g/day
Endocrine Society [28]	2013	35–45%[a]
CDA [29]	2013	40–50%[a]
DDG-DGGG [30]	2014	40–50%[a] 15–30 g for breakfast

Abbreviations AND: Academy of Nutrition and Dietetics, ADA: American Diabetes Association, CDA: Canadian Diabetes Association, DGG-DGGG: German Diabetes Association and German Association for Gynaecology and Obstetrics, CHO: carbohydrates, DRI: Dietary reference intakes, NR: not reported

[a]% of total daily calories

[b]Derived from Moreno-Castilla et al. [26]

than 45% of total daily calories, while the Endocrine Society [28] advocates for a CHO content of 35–45% of the total calories. The Canadian Diabetes Association [29] and the German Diabetes Association and German Association for Gynaecology and Obstetrics [30] established energy from CHO in an interval that ranges from 40 to 50%. Thus, the range of recommended energy from CHO is wide (from 35 to 50%), depending on the guidelines. Nevertheless, as some authors concluded [31], evidence could not be extended to Asian countries because the studies were primarily from Western countries.

Conclusions

There is not enough evidence to recommend a particular amount of CHO neither for the general pregnant population nor for pregnant women with GDM. However, Feinman et al. [11], in a critical review, supported a low-CHO diet as the first treatment strategy for type 2 diabetes and the most effective MNT, together with pharmacological treatment for type 1 diabetes.

Nevertheless, maternal glycaemia is not only affected by the CHO content. Furthermore, the GI alone does not reflect the real impact of CHO consumed. We do not eat only CHO with a specific GI, and the context has to be considered. We eat real foods in which the CHO content and the GI, among other nutritional factors, determine the maternal glucose response and, thus, perinatal outcomes. The control of GL would be a better approach to measuring the real impact of maternal diet on GDM; therefore, the RCT testing of low-GL diets are needed. In addition, it is important to consider CHO distribution throughout the day.

Furthermore, there is a possibility that other dietary factors, such as fat or protein, can play a part in the metabolic control of GDM, foetal growth and obstetric results. Therefore, these RCTs should include these outcomes.

When insulin therapy has to be introduced in GDM, it is difficult to determine whether the diet failed or the pregnant woman did not correctly follow it. Thus, it is important to not only elucidate the proper diet for GDM but also to check that it is being fully applied. It is for this reason qualified dietitians are needed. The ADA recommends again, with the highest level of evidence, that registered dietitians should be the healthcare professionals providing MNT to individuals with type 1 and type 2 diabetes [17]; however, their expertise is also important in GDM, as some authors have reported [32].

The knowledge of the best dietary GL and CHO distribution for GDM would result in cost savings, given the potential prevention of pharmacological treatment.

References

1. Peterson CM, Jovanovic-Peterson L. Percentage of carbohydrate and glycemic response to breakfast, lunch, and dinner in women with gestational diabetes. Diabetes. 1991;40(Suppl 2):172–4.
2. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Australian carbohydrate intolerance study in pregnant women (ACHOIS) trial group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477–86.
3. Metzger E, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al, HAPO Study Cooperative Research Group, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002.
4. Langer O, Yogev Y, Most O, Xenakis EMJ. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol. 2005;192:989–97.
5. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity. Diabetes. 2000;49:2208–11.
6. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, et al. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes. 1991;40(Suppl 2):S121–5.
7. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diab Care. 2007;30(Suppl 2):S251–60.
8. Tundidor D, García-Patterson A, María MA, et al. Perinatal, maternal and neonatal outcomes in women with gestational diabetes mellitus according to fetal sex. Gend Med. 2012;9:411–7.
9. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. Eunice Kennedy Shriver national institute of child health and human development maternal-fetal medicine units network. N Engl J Med. 2009;361:1339–48.
10. Panel on dietary reference intakes for macronutrients. Institute of Medicine. Dietary carbohydrates: sugars and starches. In: Dietary reference intakes: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients).Washington, DC: National Academy Press; 2005. p. 265–338.
11. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach iin diabetes management: critical review and evidence base. Nutrition. 2015;31:1–13.
12. Jenkins DJA, Wolever TMS, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362–6.
13. Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diab Care. 1997;20:545–50.
14. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011;93:984–6.
15. Brand-Miller J, Holt SH, Petocz P. Reply to R. Mendosa (letter).Am J ClinNutr. 2003;77:994–5.
16. Reader DM. Medical nutrition therapy and lifestyle interventions. Diab Care. 2007;30(Suppl 2):S188–93.
17. American Diabetes Association. Strategies for improving care. Sec. 1. In Standards of medical care in diabetes 2016. Diab Care. 2016;39(Suppl 1):S13–22.
18. Nolan CJ. Improved glucose tolerance in gestational diabetic women on a low fat, high unrefined carbohydrate diet. Aust NZ J Obstet Gynaec. 1984;24:174–7.
19. Major CA, Henry MJ, De Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol. 1998;91:600–4.
20. Romon M, Nuttens MC, Vambergue A, Vérier-Mine O, Biausque S, Lemaire C, et al. Higher carbohydrate intake is associated with decreased incidence of newborn macrosomia in women with gestational diabetes. J Am Diet Assoc. 2001;101:897–902.
21. Cypryk K, Kaminska P, Kosinski M, Pertynska-Marczewska M, Lewinski A. A comparison of the effectiveness, tolerability and safety of high and low carbohydrate diets in women with gestational diabetes. Endokrynol Pol. 2007;58:314–9.
22. Moreno-Castilla C, Hernandez M, Bergua M, Alvarez MC, Arce MA, Rodriguez K, et al. Low-carbohydrate diet for the treatment of gestational diabetes mellitus. Diab Care. 2013;36:2233–8.
23. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis. 2000; 150(2):227–43.
24. Hernandez TL, Van Pelt RE, Anderson MA, Daniels LJ, West NA, Donahoo WT, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. Diab Care. 2014;37:1254–62.
25. Hernandez TL, Van Pelt RE, Anderson MA, Reece MS, Reynolds RM, de la Houssaye BA, et al. Women with gestational diabetes randomized to a higher-complex carbohydrate/low-fat diet manifest lower adipose tissue insulin resistance, inflammation, glucose, and free fatty acids: a pilot study. Diab Care. 2015;1–4. Epub 2005 Jul 29.

26. Moreno-Castilla C, Mauricio D, Hernandez M. Role of medical nutrition therapy in the management of gestational diabetes mellitus. Curr Diab Rep. 2016;16:22.
27. Thomas AM, Gutierrez YM. American dietetic association guide to gestational diabetes mellitus. Chicago, IL: American Dietetic Association; 2005. [cited 2016 Jun 15]. Available from http://www.eatright.org/Public/ProductCatalog/SearchableProducts/104_20728.cfm.
28. Blumer I, Hadar E, Hadden DR, Jovanovic L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98:4227–49.
29. Thompson D, Berger H, Feig D, Gagnon R, Kader T, Keely E, et al. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Clinical practice guidelines: diabetes and pregnancy. Can J Diab. 2013;37: S168–83.
30. Kleinwechter H, Schäfer-Graf U, Bührer C, Hoesli I, Kainer F, Kautzky-Willer A, et al. Gestational diabetes mellitus (GDM) diagnosis, therapy and follow-up care. Practice guideline of the German Diabetes Association (DDG) and the German Association for Gynaecology and Obstetrics (DGGG). Exp Clin Endocrinol Diab. 2014;122:395–405.
31. Yusof BNM, Firouzi S, Shariff ZM, Mustafa N, Ismail NAM, Kamaruddin NA. Weighing the evidence of low glycemic index dietary intervention for the management of gestational diabetes mellitus: an Asian perspective. Int J Food Sci Nutr. 2014;65(2):144–50.
32. Reader D, Splett P, Gunderson EP. Impact of gestational diabetes mellitus nutrition practice guidelines implemented by registered dietitians on pregnancy outcomes. J Am Diet Assoc. 2006;106:1426–33.

Chapter 21
Using the Food Metabolome to Understand the Relationship Between Maternal Diet and Gestational Diabetes

Jamie V. de Seymour, Elizabeth McKenzie and Philip Baker

Key Points

- Maternal diet has been associated with GDM and dietary modifications are a good target for interventions during pregnancy to prevent GDM development or progression.
- To better understand the relationship between maternal diet and GDM, an objective form of dietary assessment and insight into metabolic mechanisms is necessary.
- Metabolomics is an analytical approach that could be used to identify dietary biomarkers of GDM, and lead to personalised nutrition for the prevention of GDM.
- The "food metabolome" is the sum of the detectable metabolites found in the human system as a result of the ingestion and digestion of food components.
- Investigations of the food metabolome in GDM could result in dietary biomarker discovery and elucidate metabolic mechanisms underpinning the relationship between maternal diet and GDM.
- Biological samples to consider for analysis include blood, urine, amniotic fluid, saliva, hair and breath.
- Many factors influence the outcome of metabolomic analyses and care must be taken when designing a study of the food metabolome, e.g. storage of samples, collection of fasted samples, time between storage and analysis.
- Different analytical platforms can be used to analyse the food metabolome [e.g. nuclear magnetic resonance, mass spectrometry coupled to chromatographic separation (gas chromatography, liquid chromatography)], each has its own strengths. Using a combination of different platforms and extraction techniques will provide a more comprehensive view of the metabolome.

Keywords Gestational diabetes · Maternal diet · Nutrition · Metabolomics · Food metabolome

Abbreviations

CVD	Cardiovascular disease
FFQ	Food frequency questionnaire
GC-MS	Gas chromatography—mass spectrometry
GDM	Gestational diabetes mellitus

J.V. de Seymour (✉) · E. McKenzie
Liggins Institute, The University of Auckland, Building 505, 85 Park Road, Grafton, Auckland, New Zealand
e-mail: j.deseymour@auckland.ac.nz

E. McKenzie
e-mail: liz.mckenzie@auckland.ac.nz

P. Baker
College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester 7RH, UK
e-mail: philip.baker@le.ac.uk

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_21

LC-MS Liquid chromatography—mass spectrometry
NMR Nuclear magnetic resonance
RCT Randomised controlled trial
SOP Standard operating procedure

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as a carbohydrate intolerance that is first recognised during pregnancy [1]. The metabolic response of the mother to carbohydrate ingestion becomes dysregulated and results in maternal hyperglycaemia, which affects the developing foetus. An influx, or continually high exposure of glucose to the foetus demands a foetal response. This response involves an increased production of foetal insulin to cope with metabolising the additional glucose load. The excess insulin production can result in hyperinsulinaemia in the foetus and lead to long-term dysregulated metabolism of the infant, increasing their risk of problems in later life due to reduced insulin sensitivity, along with disturbed pancreatic beta cell functioning [2]. GDM is associated with a multitude of other adverse consequences, in the short and long term, for both mother and offspring (Table 21.1) [3]. In addition, GDM is a contributor to the 'vicious diabetes cycle'; the development of GDM is associated with an increased risk of the mother and offspring developing type 2 diabetes and the offspring becoming obese in later life; maternal obesity is a well-known risk factor for developing GDM during gestation, and therefore the cycle of diabetes repeats (Fig. 21.1). Both mother and offspring are also at risk of developing cardiovascular disease (CVD), the leading cause of death worldwide [4]. The costs of non-communicable diseases including diabetes, metabolic syndrome and CVD has been estimated at upwards of 1.5 trillion dollars annually [5]. Reducing the rates of these chronic diseases by targeting interventions at the earliest life stage possible (in utero), would be a commendable achievement for preventative medicine. The development of strategies to reduce the long-term consequences of GDM could improve health outcomes, reduce the associated burden on healthcare costs, and result in a more productive society.

The prevalence of GDM is difficult to ascertain, as diagnosis strategies are not standardised and many countries do not practise universal screening. In New Zealand, the rates of GDM are as high as 19% in high-risk populations (Indian ethnicity) and prevalence has increased by more than fourfold in just 10 years [6]. The 2015 International Diabetes Federation report [7] claims that one in seven births is affected by GDM. Established clinical risk factors for GDM include a high BMI, advanced maternal age, family history of diabetes, and history of GDM in a previous pregnancy. Despite the extensive research that has been performed on GDM, early pregnancy screening tools to predict those at risk of GDM development, beyond the clinical indicators listed, lack validity and specificity [8].

Table 21.1 The adverse consequences associated with the development of Gestational Diabetes Mellitus

Short-term	Long-term
Macrosomia and birth complications	Infant obesity
Newborn respiratory distress syndrome	Cardiovascular disease
Preterm birth	Metabolic syndrome
Newborn hypoglycaemia	Type 2 diabetes (mother and offspring)
	Cognitive impairment of offspring

Reference: [3]

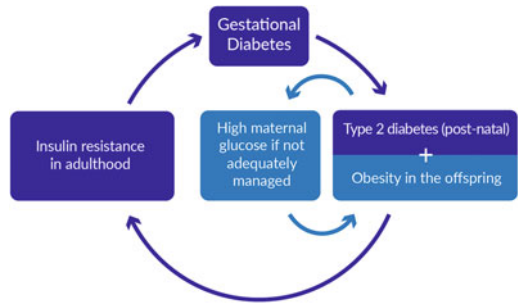


Fig. 21.1 The diabetes cycle

Without early identification, the application of preventative strategies is restricted to women that can be identified solely on the clinical characteristics mentioned above. Research in Singapore has shown that GDM screening of only individuals identified as high-risk can result in under-diagnosis. The study, which was conducted in a multi-ethnic Asian cohort from Singapore, found that conventional screening failed to detect almost half of all GDM cases confirmed by universal screening [9]. A robust early pregnancy screening tool would ensure the identification of women at risk of developing GDM at an earlier stage than current diagnostic tests, allowing for implementation of preventative strategies before high circulating maternal blood sugar had accumulated.

Maternal Diet and Gestational Diabetes Mellitus

Numerous studies have been conducted to explore the relationship between maternal diet and GDM [10–16]. These include associations with micronutrient and macronutrient composition of the diet, food item and food group associations, and complete dietary patterns (Table 21.2) [17–31].

Despite considerable efforts to understand the relationship, the evidence remains inconclusive and in some cases, conflicting (e.g. Vitamin D in Baker et al. [22], Lacroix et al. [24], and Nobles et al. [25]; Table 21.2). More recently, there has been a change in the way these associations are being addressed, opting for a food-based approach; exploring the relationship between whole foods or food groups and complete dietary patterns, as opposed to addressing nutrients in isolation. Not only does this approach take into account the synergy of nutrient intakes and their importance in combination, but it also concerns food items and food groups that are typically consumed in the population of interest, and the food matrix the nutrients are contained within, rather than looking at individual nutrients. A lack of cohesion in findings from GDM-related nutrition research may also be a reflection that there is no 'one size fits all' approach to dietary associations in the development of GDM. Dietary diversity has increased over time and as a result, there is a large difference in dietary intake between populations and even individuals within a population [32]. This diversity in consumption makes it difficult to determine population-wide recommendations and implement successful blanket dietary advice. The gut microbiome has also been recognised as playing an important role in the processing and utilisation of nutrients from the diet [33]. Gut microbiome variation between individuals will affect how they process foods; meaning that in some cases, even if diet consumption was similar between individuals, their response to that diet may be dramatically different. A shift in the public health paradigm to a personalised approach may be the way forward for dietary prevention and management of GDM.

Table 21.2 A sample of the reported associations between maternal diet and GDM since the year 2010

Authors (Year)	Dietary component	Participants	Assessment	Findings
Hekmat et al. [17]	Retinol	Iran: 41 GDM cases 41 controls	Serum levels	Lower in GDM cases
Bartáková et al. [18]	Thiamine (Vitamin B1)	Czech Republic: 99 GDM cases 78 controls	Plasma levels	Lower in GDM cases (adjusted for BMI)
Darling et al. [19]	Iron	USA/Canada: 316 GDM cases 6913 controls	58-item food frequency questionnaire (FFQ)	Preconception dietary non-heme iron intake associated with lowered risk of GDM
Bowers et al. [20]	Iron	USA: 876 GDM cases 12,599 controls	133-item semi-quantitative FFQ	Preconception intake of heme iron associated with increased risk of GDM
Zhu et al. [21]	Folic Acid	China: 249 GDM cases 1689 controls	Not specified	Folic acid Supplementation in first trimester associated with an increased GDM risk
Baker et al. [22]	Vitamin D	USA: 60 GDM cases 120 controls	Serum 25(OH)D	Vitamin D status was not associated with GDM
Yap et al. [23]	Vitamin D	Australia: 89 high dose vitamin D (5000 IU) 90 low dose (400 IU) vitamin D	RCT high or low dose vitamin D supplement daily starting in early gestation	High dose vitamin D supplementation did not improve glucose levels in pregnancy
Lacroix et al. [24]	Vitamin D	Québec: 54 GDM cases 655 controls	Blood levels of 25OHD2 and 25OHD3	Low levels of 25OHD in first trimester associated with higher risk of GDM development
Nobles et al. [25]	Vitamin D	USA: 14 GDM cases 135 controls	Serum total 25(OH) D levels	Higher 25(OH)D was associated with an increased risk of gestational diabetes Mellitus in Hispanic women
Bowers et al. [26]	Fat	USA: 860 GDM cases 12,615 controls	133-item semi-quantitative FFQ	Higher intake of cholesterol, animal fat, and MUFA in preconception was associated with increased risk of GDM
Barbieiri et al. [27]	Fat	Brazil: 151 GDM cases 648 controls	2 non-consecutive day 24-hour dietary recalls	Higher levels on the thrombogenicity indices (TI) were associated with an increased likelihood of GDM, and higher hH indices (ratios of hypo-and hypercholesterolemic fats) were associated with a lower likelihood of GDM
D'Anna et al. [28]	Myo-inositol	Italy (all women had BMI > 30): 110 treatment group 110 placebo	RCT (2 g twice a day) from first trimester until delivery	Women in the treatment group were significantly less likely to develop GDM (14% vs 33.6%)

(continued)

Table 21.2 (continued)

Authors (Year)	Dietary component	Participants	Assessment	Findings
He et al. [29]	Dietary Patterns	China: 544 GDM cases 2519 controls	64-item FFQ	A vegetable based dietary pattern was associated with a decreased risk of GDM and a sweets and seafood based dietary pattern was associated with an increased risk of GDM
Bao et al. [30]	Potatoes	USA: 854 GDM cases 20,839 controls	Questionnaire	Total consumption of potatoes pre-pregnancy demonstrated a positive, significant associated with an increased risk of GDM
Karamanos et al. [31]	Dietary Pattern	10 different Mediterranean countries (Algeria, France, Greece, Italy, Lebanon, Malta, Morocco, Serbia, Syria and Tunisia): 95 GDM cases 908 controls	78-question FFQ	An association was found between increased adherence to a Mediterranean dietary pattern and reduced likelihood of GDM development

References [3, 17–30]

Metabolomics

Metabolomics, the study of low-weight (<1 KDa) organic molecules originating from metabolic processes [34], is a promising tool for personalised nutrition. The metabolome (the complete set of low-weight organic molecules in an organism) operates at the phenotypic level (Fig. 21.2), and is also affected by diet, lifestyle factors, and environment (e.g. pollutants or food contaminants). This reflection of both genetics of an individual, as well as the environment they are in, provides a snapshot of an individual's phenotype. The human metabolome is thought to contain more than 40,000 metabolites, including fatty acids, amino acids, organic acids, nucleic acids, sugars, sugar alcohols, ketones and some vitamin derivatives [35]. Metabolomics aims to identify as many metabolites present in a biological sample as possible. The metabolomic approach is untargeted and explorative in nature and used to detect associations between disease conditions and changes in the metabolite profile by applying an empirical scientific approach, whereby the data drives hypothesis generation. The metabolite profile of the species or sample group under investigation is acquired, and rather than comparing a selection of specific compounds, the whole profile is compared with profiles of other individuals, or within an individual over time. Applications of metabolomics include biomarker discovery, mechanistic studies, drug safety, food toxicity, disease, and the assessment of dietary interventions [36–40]. Previous studies that have used metabolomic analysis for biomarker discovery in the field of pregnancy complications have been in the areas of foetal growth restriction and preeclampsia [41, 42], with some preliminary findings in the area of GDM (refer to Chap. 10).

Despite preliminary findings, biomarker studies in GDM have failed to produce a consistent set of metabolites that are clinically useful for predicting GDM development. One of the major limitations in this area of research is that there is a lack of standardised methods, and different analytical and statistical approaches have been employed, making it difficult to compare findings between studies. Additionally, GDM biomarker studies to date have predominantly been conducted on small,

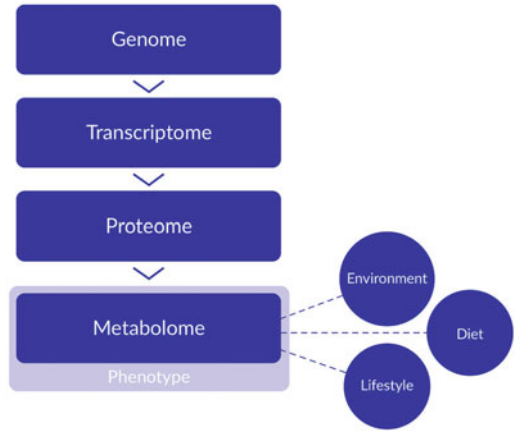


Fig. 21.2 The metabolome

heterogeneous sample populations. Large cohort studies are necessary to validate findings and establish a robust metabolite model for predicting GDM in pregnancy. Despite not yet identifying fully validated biomarkers of GDM, results generated thus far offer information which could assist with directing future research.

The Food Metabolome

The food metabolome is a term that has been created since the rise in popularity of metabolomic approaches to answering questions about food and nutrition. The food metabolome is defined by Scalbert et al. [43] as the "*part of the human metabolome directly derived from the digestion and biotransformation of foods and their constituents*". Metabolomic analyses have been shown to be sensitive to supplementation and dietary intervention, with nutrition-related research as varied as studies in lipid profiling after supplementation of a plant sterol-enriched, yoghurt drink [44] through to studies on pre-term infant breastmilk [45]. Studies of the food metabolome have identified metabolomic markers of citrus food intake, coffee, walnuts, cocoa products and even a Mediterranean dietary pattern [46–50]. Exploring the human body's metabolomic response to the consumption of different foods, nutrients and dietary patterns helps us to understand the role that our diet plays in our metabolism. The insight that the food metabolome provides gives rise to the opportunity to objectively investigate relationships between dietary intake and disease. The food metabolome can also be used for assessing why subgroups of participants react to the same foods differently to others. Despite the large amount of research that has been conducted on the food metabolome to date, no studies have investigated the association between the food metabolome and disorders of pregnancy. Pregnancy nutrition is an area of research which for many reasons is difficult to employ tightly controlled RCTs (ethics, participant acceptance and adherence, cost) and as a result, relies heavily on observational studies to identify associations with disease. Research conducted on maternal diet would greatly benefit from the application of a technique that could objectively investigate the relationship between dietary intake and pregnancy outcome.

Untapped Potential—Linking the Food Metabolome to Gestational Diabetes Mellitus

The majority of evidence for the association between maternal diet and GDM has been formed from observational research. Research of this nature is subject to bias (recall, social desirability) and results are burdened by confounders. The gold standard of scientific enquiry to determine a causal relationship is from results of placebo-controlled, double-blinded, randomised controlled trials. In order to conduct randomised controlled trials in nutrition, only one nutrient or a small selection of nutrients is chosen, based on observational evidence of that nutrient being associated with the outcome of interest. In most cases, to manipulate that chosen nutrient, a supplement (or placebo) is added to the diet. However, by doing this the research team is introducing an artificial source of the nutrient, out of its food matrix, and essentially undermining the importance of the other nutrients from foods it is commonly consumed in conjunction with. With this in mind, it is hardly surprising that randomised controlled trials of nutrients related to GDM fail to reproduce the findings of observational studies. To understand the plethora of observational findings linking maternal diet with GDM requires understanding of how the foods, dietary patterns and nutrients consumed in a typical, everyday situation may be affecting metabolism, and how they are related to the dysregulation associated with gestational diabetes. The food metabolome provides a way to objectively explore this question. Performing metabolomics on biological samples and analysing the intersect between the metabolomic profile associated with GDM and the food metabolome bridges the gap between observational associations and biological understanding of how diet is affecting metabolism, and in turn, is related to GDM development.

There are two approaches to utilising the food metabolome in investigations of the maternal diet and GDM. The first is to relate metabolomic markers of GDM to markers of dietary intake using the food biomarker literature. However, the selection of foods with established biomarkers is limited, and are unlikely to satisfactorily represent all food items consumed in a population of interest. In such a young field of research it is not known whether markers are transferable from the population they were discovered into populations of different age, ethnicity and life stage (e.g. pregnancy/menopause/adolescence). It is well known that populations respond to foods differently, hence the need to explore individualised diet solutions [51, 52].

An alternative approach is to use metabolomic biomarkers of GDM which have been identified in a population and look for associations with dietary assessments in the same population. The metabolome can be analysed using different techniques and it is important to employ a technique that ensures the GDM biomarkers and dietary biomarkers overlap. Finding an analytical technique that can identify both GDM biomarkers and dietary biomarkers in the same participants will ensure that there is a greater potential for finding associations. Once potential biomarkers are identified, biochemical pathway analysis can be carried out to determine the metabolic mechanisms linking dietary intake to disease outcome.

The long-term goal of this endeavour is to develop a personalised pregnancy screening test that uses a biological specimen (e.g. blood/urine/faeces/hair) to objectively identify the consumption of dietary components that are associated with the development of GDM. Following identification of the dietary components, tailored dietary advice would be generated to assist with the prevention of GDM development. Unlocking this relationship would be a revolutionary step forward for preventative, personalised nutrition and would greatly increase the scope of metabolomic applications.

Factors Affecting the Use of Metabolomics for Linking Diet and Gestational Diabetes

To unleash the potential of the food metabolome in understanding the relationship between maternal diet and GDM, there are some research and clinical factors that need to be addressed.

The first consideration is the sample type and analytical platform. It is important to ensure that samples have been collected and stored appropriately for metabolomic analysis, and this will differ depending on the specimen chosen. Some important questions that should be asked when choosing samples, particularly if selecting from a biobank rather than designing an experiment from scratch are:

(1) What was the time between sample collection and storage?
(2) Were the samples stored at the correct temperatures?
(3) Were the participants fasted at time of collection?
(4) Was a well-designed, reproducible protocol/Standard Operating Procedure (SOP) followed?

Samples collected for analysis will be compared against other samples (research setting comparisons of cases vs controls) or reference levels (clinical setting), so it is important that procedures are standardised and reproducible, to allow for valid comparisons. It is also necessary to consider which type of analytical technique is best suited to identifying the metabolites of interest. Both Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS) techniques are used in metabolomics research. NMR is used predominantly for non-targeted analyses whereas the high sensitivity that can be achieved with MS makes it suited to both non-targeted and targeted analyses. The major advantages of NMR include its ability to analyse metabolites with very little sample preparation, and non-destructive analysis. By contrast, the major advantages of MS technologies are high sensitivity and the ability to identify a larger amount of compounds, however, the sample is destroyed during analysis [53]. In terms of the clinical application, MS technologies are cheaper to run, tend to require less space and are more often found in hospitals than NMR-based instruments. Chromatographic separation techniques are often coupled to MS technologies, most commonly liquid chromatography (LC) or gas chromatography (GC) are used. GC-MS systems are more affordable than LC-MS, however, GC-MS requires the metabolites in the sample to be volatile for analysis and it is therefore limited to analysing naturally volatile metabolites, or metabolites that can be chemically derivatised to increase their volatility. GC-MS separation performs the best on less polar species, whereas polar species are more compatible with LC-MS analysis. No single analytical platform is able to detect the full range of metabolites present in a biological specimen. Each platform has its strengths and limitations. Using a combination of techniques allows for a greater range of metabolites to be identified, however, this requires time, expertise and funds.

An equally important consideration for metabolomic profiling is which type of biological sample to analyse. In a pregnant woman, the placenta or amniotic fluid will inform a researcher about the environment the foetus is being exposed to during gestation. However, amniocentesis is a procedure that requires specific expertise and poses some risks, and therefore should not be conducted without strong evidence of benefits [54]. Although it may be an excellent specimen for investigating mechanisms in a research setting, it is not appropriate to use as the specimen in a screening test. By contrast, urine is a widely used specimen in dietary and metabolomic research due to its ease to obtain, and minimal processing required to extract metabolites, when compared to other specimens such as tissue and blood. Due to its polarity, urine is the specimen most likely to containing non-nutrient components from cooking, storage or the gut microbiome [55]. Non-nutrient components are a confounding factor in dietary metabolomics studies as they affect the metabolome and complicate the interpretation of dietary metabolomic results. Theoretically, one way to minimise the interference of non-nutrient components is to analyse blood samples. Blood (in the form of plasma

and serum) is currently the most likely candidate for dietary metabolomics analyses. Despite blood collection being more invasive than urine collection, it is a common procedure that currently poses very little risk in a trained environment. The plasma/serum metabolome represents the sum total of metabolism from multiple sources in the body and therefore provides an integrated view of metabolism. The main limitation of analysing blood, rather than single cells, is that it is difficult to determine which organ or system is dysregulated. However, for the purpose of biomarker discovery and screening test development, identifying the source of dysregulation is not necessary. Another factor to consider where blood samples are concerned, is whether participants are fasted prior to collection. Non-fasted samples are disproportionately affected by the last meal consumed, masking the underlying metabolic processes.

Alternative biological samples for consideration include breath, saliva and hair. Breath and saliva have both been used as specimens for metabolomic investigations into diet, demonstrating some success in discriminating between different dietary behaviours [56, 57]. However, to date, neither have been used successfully to detect biomarkers of GDM. Hair has been used as a specimen for metabolomic biomarker studies of pregnancy disorders [58, 59], with He et al. [59] identifying a potential biomarker for discriminating GDM cases and controls. Hair analysis potentially offers insight into metabolism over a much longer time period than blood or urine. Hair grows at a rate of approximately 1 centimetre per month [60] so a strand of maternal hair as short as 12 cm long may represent the metabolome averaged over a year, or more, depending on the rate of growth. Ideally the hair should be sectioned according to the approximate time frame of interest, and could thus provide pregnancy-specific information. Hair has been used to successfully identify dietary heterogeneity in a sample of participants from Western Europe and the United States of America [61] which demonstrates its promise as a non-invasive specimen type for objectively analysing maternal diet. However, metabolomic hair analysis is still in its infancy, and requires further validation before it can be considered a reliable matrix for biomarker exploration.

Cost and complexity of metabolomic analyses are often a limiting factor for the use of metabolomics in the nutrition field [55]. However, the development of new technology, software, and the recognition of the benefits to the field, has advanced research in this area. Metabolomics could prove to be a more time-efficient and less subjective alternative to dietary intake investigations and biochemical assays routinely used in nutrition studies [62, 63]. However, there are some ethical and social considerations that need to be explored when assessing the use of metabolomics as a screening tool for personalised dietary advice in a clinical setting. The cost of universal metabolomic screening in pregnancy needs to be taken into account. Without public health initiatives or financial support, this endeavour will become a privately funded, personalised nutrition venture. Becoming a private investment restricts access of services only to mothers that can afford to pay for the service, and that have been educated on its availability. This risks growing the health inequality gap, especially given that GDM prevalence, along with many other disorders of pregnancy, are higher in lower socioeconomic groups [64, 65].

Conclusion

Gestational diabetes is a growing concern worldwide. The best defence against the adverse consequences associated with GDM is early identification of risk and implementation of preventative strategies. Maternal nutrition is an obvious target for prevention strategies as it is non-invasive, accessible and seen favourably by expectant mothers as a safer alternative to other interventions. Despite a large body of research demonstrating a relationship between maternal diet and GDM, the evidence remains inconsistent. Metabolomics provides an opportunity to reveal associations between maternal diet and GDM, through analysing the metabolome at the intersect between GDM risk and

maternal diet. Utilising the metabolome in this way allows for the identification of diet-linked biomarkers of GDM, as well as possible elucidation of mechanisms underpinning dietary associations to GDM development. Unlocking this information would revolutionise the development of dietary interventions to prevent GDM and its associated consequences.

References

1. Buchanan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115(3):485–91. doi:10.1172/JCI24531.
2. Jovanovic L. The role of continuous glucose monitoring in gestational diabetes mellitus. Diab Technol Ther. 2000;2(supplement 1):67–71. doi:10.1089/15209150050214159.
3. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2010;23(3):199–203. doi:10.3109/14767050903550659.
4. World Health Organisation (WHO). Cardiovascular diseases (CVDs). http://www.who.int/mediacentre/factsheets/fs317/en/. Published 2016.
5. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, Prettner K, Rosenberg L, Seligman B, Stein AZ, Weinstein C. The global economic burden of noncommunicable diseases. Geneva: World Economic Forum; 2011.
6. Pot M, Sadler L. National Women's Annual Clinical Report 2013; 2013. http://nationalwomenshealth.adhb.govt.nz/Portals/0/AnnualReports/ACR_Master_Appendix__1to12_2013_LYNNAUGUST1plusMP.pdf.
7. International Diabetes Federation. IDF Diabetes Atlas: Seventh Edition; 2015. http://www.diabetesatlas.org/resources/2015-atlas.html.
8. Correa PJ, Vargas JF, Sen S, Illanes SE. Prediction of gestational diabetes early in pregnancy: targeting the long-term complications. Gynecol Obstet Invest. 2014;77(3):145–9. doi:10.1159/000357616.
9. Chong Y-S, Cai S, Lin H, et al. Ethnic differences translate to inadequacy of high-risk screening for gestational diabetes mellitus in an Asian population: a cohort study. BMC Pregnancy Childbirth. 2014;14:345. doi:10.1186/1471-2393-14-345.
10. Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Cochrane database of systematic reviews. Chichester, UK: Wiley; 2015. doi:10.1002/14651858.CD011507.pub2.
11. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr. 2011;94(6_Suppl):1975S–1979S. doi:10.3945/ajcn.110.001032.
12. Zhang C, Schulze MB, Solomon CG, Hu FB. A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus. Diabetologia. 2006;49(11):2604–13. doi:10.1007/s00125-006-0422-1.
13. Zhang C, Liu S, Solomon CG, Hu FB. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. Diab Care. 2006;29(10):2223–30. doi:10.2337/dc06-0266.
14. Oostdam N, van Poppel MNM, Wouters MGAJ, van Mechelen W. Interventions for preventing gestational diabetes mellitus: a systematic review and meta-analysis. J Women's Heal. 2011;20(10):1551–63. doi:10.1089/jwh.2010.2703.
15. Madhuvrata P, Govinden G, Bustani R, Song S, Farrell T. Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials. Obstet Med. 2015;8(2):68–85. doi:10.1177/1753495X15576673.
16. Poel YHM, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: A systematic review and meta-analysis. Eur J Intern Med. 2012;23(5):465–9. doi:10.1016/j.ejim.2012.01.007.
17. Hekmat K, Bagheri R, Abedi P, Tabesh H. The relationship of fat soluble antioxidants with gestational diabetes in Iran: a case-control study. J Matern Fetal Neonatal Med. 2014;27(16):1676–9. doi:10.3109/14767058.2014.892921.
18. Bartáková V, Pleskačová A, Kuricová K, et al. Dysfunctional protection against advanced glycation due to thiamine metabolism abnormalities in gestational diabetes. Glycoconj J. 2016;33(4):591–8. doi:10.1007/s10719-016-9688-9.
19. Darling A, Mitchell A, Werler M. Preconceptional iron intake and gestational diabetes mellitus. Int J Environ Res Public Health. 2016;13(6):525. doi:10.3390/ijerph13060525.
20. Bowers K, Yeung E, Williams MA, et al. A prospective study of prepregnancy dietary iron intake and risk for gestational diabetes mellitus. Diab Care. 2011;34(7):1557–63. doi:10.2337/dc11-0134.
21. Zhu B, Ge X, Huang K, et al. Folic acid supplement intake in early pregnancy increases risk of gestational diabetes mellitus: evidence from a prospective cohort study. Diab Care. 2016;39(3):e36–7. doi:10.2337/dc15-2389.

22. Baker AM, Haeri S, Camargo CA, Stuebe AM, Boggess KA. First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diab Metab Res Rev. 2012;28(2):164–8. doi:10.1002/dmrr.1282.
23. Yap C, Cheung NW, Gunton JE, et al. Vitamin D supplementation and the effects on glucose metabolism during pregnancy: a randomized controlled trial. Diab Care. 2014;37(7):1837–44. doi:10.2337/dc14-0155.
24. Lacroix M, Battista M-C, Doyon M, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetol. 2014;51(4):609–16. doi:10.1007/s00592-014-0564-4.
25. Nobles CJ, Markenson G, Chasan-Taber L. Early pregnancy vitamin D status and risk for adverse maternal and infant outcomes in a bi-ethnic cohort: the behaviors affecting baby and you (B.A.B.Y.) study. Br J Nutr. 2015;114(12):2116–28. doi:10.1017/S0007114515003980.
26. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C. A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. Am J Clin Nutr. 2012;95(2):446–53. doi:10.3945/ajcn.111.026294.
27. Barbieiri P, Nunes JC, Torres AG, et al. Indices of dietary fat quality during midpregnancy is associated with gestational diabetes. Nutrition. 2016;32(6):656–61. doi:10.1016/j.nut.2015.12.002.
28. D'Anna R, Di Benedetto A, Scilipoti A, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women. Obstet Gynecol. 2015;126(2):310–15. doi:10.1097/AOG.0000000000000958.
29. He J-R, Yuan M-Y, Chen N-N, et al. Maternal dietary patterns and gestational diabetes mellitus: a large prospective cohort study in China. Br J Nutr. 2015;113(08):1292–300. doi:10.1017/S0007114515000707.
30. Bao W, Tobias DK, Hu FB, Chavarro JE, Zhang C. Pre-pregnancy potato consumption and risk of gestational diabetes mellitus: prospective cohort study. BMJ. January 2016:h6898. doi:10.1136/bmj.h6898.
31. Karamanos B, Thanopoulou A, Anastasiou E, et al. Relation of the Mediterranean diet with the incidence of gestational diabetes. Eur J Clin Nutr. 2014;68(1):8–13. doi:10.1038/ejcn.2013.177.
32. Drewnowski A, Popkin BM. Lead review article the nutrition transition: new trends in the global Diet; 1997. doi:10.1111/j.1753-4887.1997.tb01593.x.
33. Flint HJ, Scott KP, Louis P, Duncan SH. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol Publ online 04 Sept 2012; doi101038/nrgastro2012156. 2012;9(10):577. doi:10.1038/NRGASTRO.2012.156.
34. Villas-Bôas SG. Metabolome analysis: an introduction. Wiley-Interscience; 2007.
35. Wishart DS, Jewison T, Guo AC, et al. HMDB 3.0–the human metabolome database in 2013. Nucleic Acids Res. 2013;41(Database issue):D801–D807. doi:10.1093/nar/gks1065.
36. Pamungkas AD, Park C, Lee S, Jee SH, Park YH. High resolution metabolomics to discriminate compounds in serum of male lung cancer patients in South Korea. 2016;17(1). doi:10.1186/s12931-016-0419-3.
37. Kim YJ, Lee HS, Kim YK, et al. Association of metabolites with obesity and type 2 diabetes based on FTO genotype. 2016;11(6). doi:10.1371/journal.pone.0156612.
38. Li Y, Ju L, Hou Z, et al. Screening, verification, and optimization of biomarkers for early prediction of cardiotoxicity based on metabolomics. 2015;14(6):2437–2445. doi:10.1021/pr501116c.
39. Inoue K, Tanada C, Hosoya T, et al. Principal component analysis of molecularly based signals from infant formula contaminations using LC-MS and NMR in foodomics. 2016:3876–3881. doi:10.1002/jsfa.7584.
40. Stradling C, Thomas GN, Hemming K, et al. Randomised controlled pilot study to assess the feasibility of a Mediterranean Portfolio dietary intervention for cardiovascular risk reduction in HIV dyslipidaemia: a study protocol. 2016;6(2). doi:10.1136/bmjopen-2015-010821.
41. Horgan RP, Broadhurst DI, Walsh SK, et al. Metabolic profiling uncovers a phenotypic signature of small for gestational age in early pregnancy. J Proteome Res. 2011;10(8):3660–73. doi:10.1021/pr2002897.
42. Kenny LC, Broadhurst DI, Dunn W, et al. Robust early pregnancy prediction of later preeclampsia using metabolomic biomarkers. Hypertens. 2010;56(4):741–749. doi:10.1161/HYPERTENSIONAHA.110.157297.
43. Scalbert A, Brennan L, Manach C, et al. The food metabolome: a window over dietary exposure. Am J Clin Nutr. 2014;99(6):1286–308. doi:10.3945/ajcn.113.076133.
44. Szymańska E, van Dorsten FA, Troost J, et al. A lipidomic analysis approach to evaluate the response to cholesterol-lowering food intake. Metabolomics. 2012;8(5):894–906. doi:10.1007/s11306-011-0384-2.
45. Marincola FC, Noto A, Caboni P, et al. A metabolomic study of preterm human and formula milk by high resolution NMR and GC/MS analysis: preliminary results. J Matern Fetal Neonatal Med. 2012;25(Suppl 5):62–7. doi:10.3109/14767058.2012.715436.
46. Heinzmann SS, Brown IJ, Chan Q, et al. Metabolic profiling strategy for discovery of nutritional biomarkers: proline betaine as a marker of citrus consumption. Am J Clin Nutr. 2010;92(2):436–43. doi:10.3945/ajcn.2010.29672.
47. Rothwell JA, Fillâtre Y, Martin J-F, et al. New biomarkers of coffee consumption identified by the non-targeted metabolomic profiling of cohort study subjects. Ashida H, ed. PLoS ONE. 2014;9(4):e93474. doi:10.1371/journal.pone.0093474.

48. Garcia-Aloy M, Llorach R, Urpi-Sarda M, et al. A metabolomics-driven approach to predict cocoa product consumption by designing a multimetabolite biomarker model in free-living subjects from the PREDIMED study. Mol Nutr Food Res. 2015;59(2):212–20. doi:10.1002/mnfr.201400434.
49. Garcia-Aloy M, Llorach R, Urpi-Sarda M, et al. Novel multimetabolite prediction of walnut consumption by a urinary biomarker model in a free-living population: the PREDIMED study. J Proteome Res. 2014;13(7):3476–83. doi:10.1021/pr500425r.
50. Vázquez-Fresno R, Llorach R, Urpi-Sarda M, et al. Metabolomic pattern analysis after mediterranean diet intervention in a nondiabetic population: a 1- and 3-year follow-up in the PREDIMED study. J Proteome Res. 2015;14(1):531–40. doi:10.1021/pr5007894.
51. Kataoka M, Venn BJ, Williams SM, Te Morenga LA, Heemels IM, Mann JI. Glycaemic responses to glucose and rice in people of Chinese and European ethnicity. Diabet Med. 2013;30(3):e101–7. doi:10.1111/dme.12080.
52. Dangin M, Guillet C, Garcia-Rodenas C, et al. The rate of protein digestion affects protein gain differently during aging in humans. J Physiol. 2003;549(2):635–44. doi:10.1113/jphysiol.2002.036897.
53. Emwas A-HM. The strengths and weaknesses of NMR spectroscopy and mass spectrometry with particular focus on metabolomics research. Methods Mol Biol. 2015;1277:161–93. doi:10.1007/978-1-4939-2377-9_13.
54. Tabor A, Madsen M, Obel E, Philip J, Bang J, Gaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet. 1986;327(8493):1287–93. doi:10.1016/S0140-6736(86)91218-3.
55. Gibney MJ, Walsh M, Brennan L, Roche HM, German B, van Ommen B. Metabolomics in human nutrition: opportunities and challenges. Am J Clin Nutr. 2005;82(3):497–503. http://www.ncbi.nlm.nih.gov/pubmed/16155259.
56. Baranska A, Tigchelaar E, Smolinska A, et al. Profile of volatile organic compounds in exhaled breath changes as a result of gluten-free diet. J Breath Res. 2013;7(3):037104. doi:10.1088/1752-7155/7/3/037104.
57. De Filippis F, Vannini L, La Storia A, et al. The same microbiota and a potentially discriminant metabolome in the saliva of omnivore, ovo-lacto-vegetarian and vegan individuals. Berg G, ed. PLoS ONE. 2014;9(11):e112373. doi:10.1371/journal.pone.0112373.
58. Sulek K, Han T-L, Villas-Boas SG, et al. Hair metabolomics: identification of fetal compromise provides proof of concept for biomarker discovery. Theranostics. 2014;4(9):953–9. doi:10.7150/thno.9265.
59. He X, de Seymour JV, Sulek K, et al. Maternal hair metabolome analysis identifies a potential marker of lipid peroxidation in gestational diabetes mellitus. Acta Diabetol. 2016;53(1):119–22. doi:10.1007/s00592-015-0737-9.
60. Pragst F, Balikova MA. State of the art in hair analysis for detection of drug and alcohol abuse. Clin Chim Acta. 2006;370(1):17–49. doi:10.1016/j.cca.2006.02.019.
61. Valenzuela LO, Chesson LA, Bowen GJ, et al. Dietary heterogeneity among western industrialized countries reflected in the stable isotope ratios of human hair. Blanc S, ed. PLoS ONE. 2012;7(3):e34234. doi:10.1371/journal.pone.0034234.
62. Scalbert A, Brennan L, Fiehn O, et al. Mass-spectrometry-based metabolomics: limitations and recommendations for future progress with particular focus on nutrition research. Metabolomics. 2009;5(4):435–58. doi:10.1007/s11306-009-0168-0.
63. van Ommen B, Stierum R. Nutrigenomics: exploiting systems biology in the nutrition and health arena. Curr Opin Biotechnol. 2002;13(5):517–21. doi:10.1016/S0958-1669(02)00349-X.
64. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol. 2000;14(3):194–210. doi:10.1046/j.1365-3016.2000.00266.x.
65. Bo S, Menato G, Bardelli C, et al. Low socioeconomic status as a risk factor for gestational diabetes; 2008 (/data/revues/12623636/00280002/139/).

Chapter 22
Probiotics in the Prevention of Gestational Diabetes Mellitus (GDM)

Luisa F. Gomez Arango, Helen L. Barrett, Leonie K. Callaway, H. David McIntyre and Marloes Dekker Nitert

Key Points

- The gut microbiota is an important determinant of metabolic health
- In pregnancy, the composition of the gut microbiota is altered
- Outside pregnancy, the composition of the gut microbiota is altered in disease states including obesity and type 2 diabetes
- Manipulation of the gut microbiota is possible through supplementation with probiotics, prebiotics, and/or synbiotics
- Probiotic supplementation may be a successful strategy to prevent the development of gestational diabetes mellitus.

Keywords Gestational diabetes mellitus · Microbiome · Metabolism · Pregnancy · Probiotics · Prebiotics · Pregnancy complications

Abbreviations

GDM	Gestational diabetes mellitus
HOMA-B	Homeostatic model assessment of beta cell function
HOMA-IR	Homeostatic model assessment of insulin resistance
Hs-CRP	High sensitivity C-reactive protein
SCFA	Short chain fatty acids
VLDL	Very low-density lipoprotein

L.F. Gomez Arango · H.L. Barrett · M.D. Nitert (✉)
School of Medicine, The UQ Centre for Clinical Research, The University of Queensland, Herston Campus, Herston, QLD, Australia
e-mail: m.dekker@uq.edu.au

L.F. Gomez Arango
e-mail: luisa.gomezarango@uq.net.au

H.L. Barrett
e-mail: h.barrett@uq.edu.au

L.K. Callaway
Faculty of Medicine, School of Medicine, RBWH Clinical School, The UQ Centre for Clinical Research, The University of Queensland, Herston Campus, Herston, QLD, Australia
e-mail: l.callaway@uq.edu.au

H. David McIntyre
School of Medicine, Mater Clinical School, The University of Queensland, South Brisbane, QLD, Australia
e-mail: h.d.mcintyre@uq.edu.auI

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_22

Introduction

Gestational diabetes mellitus (GDM) is defined as hyperglycemia first recognized during pregnancy. GDM is associated with adverse outcomes for the mother and the baby in the short term and the long term. Other chapters in this book provide an in-depth overview of different aspects of gestational diabetes including diagnostic criteria, associations with other (pregnancy) disease states, and effects of diet and bariatric surgery. In this chapter, the role of the microbiome, e.g., the composite of bacteria in different parts of the body, on the development of GDM will be discussed. The importance of the microbiome on health and disease has only recently been uncovered. In the first part of this chapter, the changes in the microbiome that are associated with the hormonal and physiological changes of pregnancy will be discussed. Since the microbiome may contribute to the development of GDM, manipulation of microbiome composition particularly in the gastrointestinal tract may be a strategy to prevent GDM. The use of probiotics (live bacteria that when taken in sufficient doses are known to have beneficial effects on the host) will be examined in relation to prevention of GDM in the second part of this chapter. Finally, there will be a short discussion on prebiotics—dietary substances that can serve as a food source for bacteria—to alter the composition of the microbiome.

Microbiome

Defining the Gut Microbiota

A microbiome comprises the collective genomes of bacteria, fungi, protozoa, and viruses that reside in a previously established environment. Humans have clusters of bacteria in multiple parts of the body, so-called microbiota, e.g., gut/oral/vaginal microbiota, etc. The gut microbiota is numerically very dense ($\sim 10^{14}$ bacteria) [1] and was previously hypothesized to outnumber human cells by a factor of 10. However, updated analyses show that the number of bacteria equals the number of human cells [2]. The gut microbiota shows large variability between individuals. Nevertheless, members of the *Firmicutes* and *Bacteroidetes* phyla constitute the majority of the human gut microbiota [3], whereas *Proteobacteria, Verrucomicobia, Actinobacteria, Fusobacteria* and *Cyanobacteria* are present in minor proportions [4]. The gut microbiota affects host physiology by (1) harvesting indigestible nutrients/energy from diet; (2) production of vitamins (e.g., vitamins K and B); (3) xenobiotic, lipid and glucose metabolism; (4) gut epithelial cell renewal; (5) immunity (e.g., maturation and development of innate and cell-mediated immunity, pathogenic response, and intestinal barrier function); and (6) human behavior [5] (Table 22.1). The microbiota can be modulated by host factors such as genetic make-up, environmental factors, such as diet and lifestyle choices (e.g., smoking, alcohol consumption, exercise), pharmaceutical agents such as antibiotics, and intake of probiotics or prebiotics [5].

A healthy human gut microbiota is associated with high-bacterial diversity whereas reduction in diversity has been linked with dysbiosis [5]. Dysbiosis is an imbalance in the microbiota structure and has been reported in a range of diseases including inflammatory bowel disease, obesity and diabetes. In this section, we shall address changes in the maternal microbiota over the course of healthy pregnancy (Fig. 22.1) and consider whether microbiome structure is affected by maternal obesity and gestational diabetes mellitus.

Table 22.1 Known functions of the gut microbiome affecting the health of the host

Function	Effects on host
Barrier function	Reduced epithelial permeability preventing endotoxemia Modulation of mucosal glycosylation
Energy supply	Energy harvesting by digestion of dietary fibers Production of short chain fatty acids
Metabolism	Modulation of glucose homeostasis, lipids and xenobiotic metabolism Biosynthesis of vitamins K, B, and folic acid Deconjugation of bile acids
Immunity	Enhance signal transduction mechanisms Inhibit pathogens colonization Activates regulatory T cells Promotes immunoglobulin production Stimulates anti-inflammatory cytokines secretion and downregulates inflammation
Behavior	Regulates mood and emotions Dysbiosis linked to autism spectrum disorder, ADHD, and anxiety/depression Infant neurodevelopment

ADHD, attention deficit hyperactivity disorder

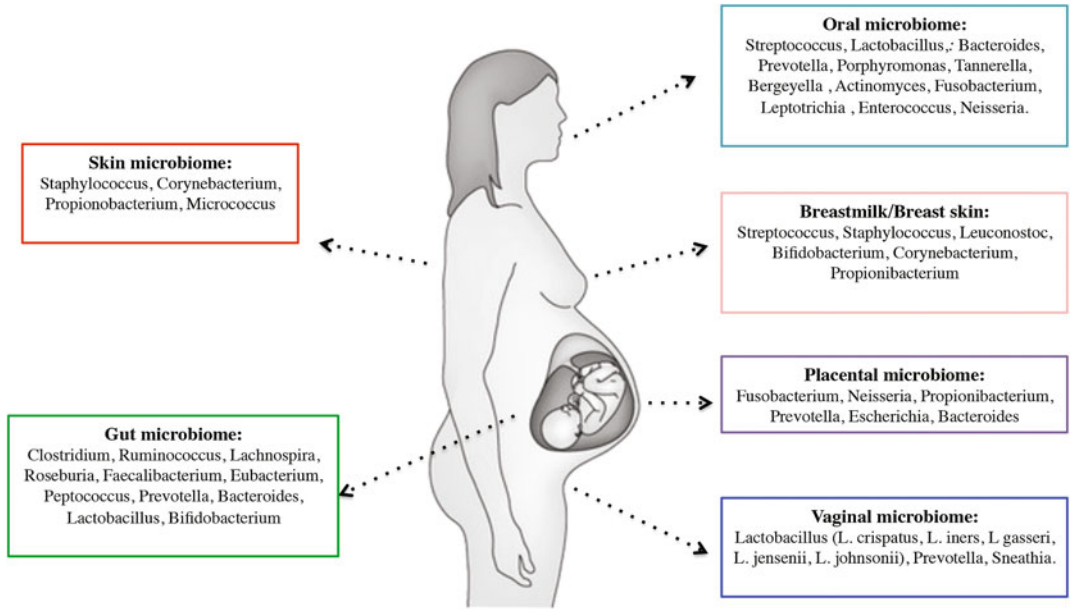


Fig. 22.1 Microbiota of pregnancy. *Legend* The main genera of the microbiota at six different body sites in pregnancy are depicted in this figure

The Maternal Gut Microbiota in Health and Disease

Maternal adaptations occur throughout pregnancy to accommodate the growing fetus. Temporary changes in gut physiology, intestinal absorption, and permeability occur during the perinatal period and highlight the importance of the gastrointestinal tract. Furthermore, pregnancy is associated with gut microbial adaptations that may impact on maternal metabolic health and contribute to the metabolic and immunological health of the baby [6].

The maternal gut microbiota undergoes profound changes during normal pregnancy with increased bacterial biomass [7]. Between the first and the third trimesters of gestation, the gut microbial composition changes [8] but thereafter remains stable during breastfeeding [9]. The first trimester microbiota resembles that of nonpregnant healthy women but with advancing pregnancy, an overall decrease in bacterial diversity develops within each woman's gut microbiota. Which species are lost is highly variable and this contributes to the high variability in microbiota composition between pregnant women in their third trimester. In addition to species loss, there is an increase in bacteria belonging to the phyla *Actinobacteria* and *Proteobacteria*, similar to the pattern observed in obesity and inflammatory bowel disease [10].

It is not clear which mechanisms give rise to the variation of the gut microbiota over pregnancy although they appear independent of maternal BMI, gestational diabetes status, diet or antibiotic intake. It has been hypothesized that hormonal and immunological changes may drive these microbial adaptations but there are currently no studies that have experimentally addressed these possible mechanisms. There is one study suggesting that the changes in the gut microbiota may drive some of the physiological changes seen in pregnancy: transplantation of third trimester fecal samples into germ-free mice resulted in insulin desensitization and increased fat mass similar to the changes observed in healthy pregnant women [8]. This suggests that during pregnancy the gut microbiota is modulated to enhance energy availability for both mother and baby. However, the data of Avershina et al., who reported no shifts in microbial composition during early and late pregnancy, do not support this suggested mechanism [11]. Mechanistic studies are needed to provide definite insights into the what drives the changes in gut microbiota composition in pregnancy.

There is accumulating evidence linking the gut microbiota to metabolic changes throughout pregnancy. However, the exact identities of the mediators of metabolic changes related to the gut microbiota are still under investigation. Short chain fatty acids (SCFA) have been proposed to serve as microbiotal mediators. SCFA are formed through fermentation of dietary fibers by gut microbiota. Microbial SCFAs yield energy for colonic cellular maintenance and may play a role as anti-inflammatory agents, growth suppressors of pathogens, promoters of apoptosis in cancer cells, and in the maintenance of intestinal homeostasis. To date there are only a few studies on SCFAs in pregnancy, partly due to the challenges of accurately measuring these volatile substances. In normal pregnancy, SCFAs levels are higher than in nonpregnant normal-weight and obese subjects [9]. This increase has been attributed to pregnancy-associated metabolic changes, increases in low-grade inflammation, and the highly efficient dietary energy extraction and prolonged gut transit in pregnancy.

Maternal Obesity

Overweight and obese women have gut microbiota dysbiosis compared to normal-weight women pre-pregnancy. These microbial alterations could persist or be further modified during pregnancy and thereby contribute to the higher risks of complications during gestation, delivery, and postpartum for overweight and obese mothers and babies [12]. An increase in *Bacteroides* and *Staphylococcus* was observed in overweight pregnant women compared to normal-weight women in a prospective follow-up study, associating *Bacteroides* abundance with excessive gestational weight gain [7]. However, increased abundance of *Bacteroides* and *Bifidobacterium* and decreased abundance of *Staphylococcus* and *E. coli* in normal-weight compared to overweight pregnant women has also been reported [13]. A similar trend of low *Bacteroides* numbers has been observed in lean nonpregnant subjects and after weight loss interventions [14]. Therefore, the gut microbiota could be a relevant target to assist weight management in pregnancy.

Maternal obesity is associated with significant changes in endocrine and metabolic function, with increased circulating levels of SCFAs in women who are obese during pregnancy [15]. Serum acetate is associated with maternal adiponectin levels and weight gain whereas low propionate concentrations are associated with maternal leptin and infant birth weight. Larger systematic studies are required to confirm the associations between SCFAs and obesity in pregnancy. Of importance, high expression of SCFAs receptors, GPR43 and GPR41, are presented in fetal membranes and placenta after the onset of labor [16]. In vitro studies have shown that treatment of placental amnion membrane explants with bacterial lipopolysaccharide (LPS) raised the expression of GPR43 but treatment with propionate lowered the inflammatory response [16]. This suggests that altered maternal circulating SCFAs may affect the baby, perhaps through the expression of these receptors in the placenta.

GDM

The gut microbiota composition may contribute to the onset of type 2 diabetes mellitus with decreased abundance of the phyla *Firmicutes,* class *Clostridia* and reduction in butyrate-producing bacteria [17]. Fecal transplants from lean healthy donors to male recipients with metabolic syndrome confirmed the causal role of the gut microbiota in insulin resistance. Six weeks after gut microbiota transplantation, insulin sensitivity improved, the abundance of the butyrate producer *Roseburia intestinalis* increased and fecal SCFA decreased [18].

There is little information on the microbiome composition in pregnant women who develop GDM. However, a distinct microbiota composition was revealed in insulin resistant women with previous GDM compared to women who had a normoglycemic pregnancy. The post-GDM group had a *Prevotellaceae*-rich microbiome with a lower abundance of *Firmicutes* [19]. Similarly, higher ratios of *Bacteroides-Prevotella* have been reported in type 2 diabetes [17]. These results support the emerging view that gut microbes can affect glucose metabolism in the host; however, larger sample sizes are required to provide definite evidence.

Vaginal Microbiota

Changes to the vaginal microbiota also occur in pregnancy. There is a decrease in bacterial diversity and richness [20, 21] but higher community stability when compared to nonpregnant subjects [22]. *Lactobacillus* species (*L. iners, L. crispatus, L. gasseri, L. jensenii,* and *L. johnsonii*) have higher prevalence at later gestational age [20, 22]. The geographic location and ethnic background may further affect the vaginal microbiota. *Lactobacillus* may promote a healthy vaginal microenvironment by lowering pH through the production of lactic acid, hydrogen peroxide, and bacteriocins limiting pathogenic infections. Dysbiosis in the vaginal microbiota and bacterial vaginosis are associated with risk for preterm birth [23] and has been suggested that higher abundance of *Gardnerella, Ureaplasma,* and lower abundance of *Lactobacillus* may be used as a predictive biomarker for preterm birth [21].

Oral Microbiota

The oral microbiota is one of the most diverse microbiomes in the human body but has not fully been explored during pregnancy. *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes,*

and *Fusobacteria* are the main phyla in the oral cavity [24]. The overgrowth of specific bacteria is associated with dental caries and periodontal disease [25]. Periodontal disease has been linked to pathologies at different body sites, this is likely due to oral bacteria having access to bloodstream [26]. Microbial transmission from the oral to the uterine cavity is a risk factor for preterm birth and low birth weight babies [27]. Specific oral strains have been correlated with intrauterine infections and preterm birth supporting evidence for oral-utero bacterial transmission. Moreover, active periodontal disease during pregnancy is associated with an increased risk in preeclampsia [28] and outside pregnancy with atherosclerosis and cardiovascular disease [29]. Outside of pregnancy, obese, and diabetic patients reported lower levels of oral *Bifidobacteria*, however, these increased tenfold after Roux-en-Y gastric bypass [30]. Whether the oral microbiota changes throughout pregnancy or is affected by maternal obesity and/or glycemic status is unknown. Little is known about the oral microbial community in newborns and whether there is a relationship with the maternal oral microbiota. Oral microbiota profiles from mother-baby dyads are needed in order to identify diagnostic biomarkers for maternal and fetal outcomes.

Placental Microbiota

In recent years, the concept that the intrauterine environment is bacteria-free has been challenged. The presence of bacterial DNA, despite the absence of culturable bacteria per se, from *Bifidobacterium* spp and *Lactobacillus rhamnosus* in human placenta has been demonstrated [31]. Murine models have shown that hematogenous infection by oral pathogenic bacteria results in colonization of the placenta with higher risk of preterm birth. In humans, preterm birth has been associated with the presence of oral bacteria in placenta as well as the presence of infectious agents in the placenta with preeclampsia. Beyond the placenta, bacterial DNA has also been detected in fetal membranes, umbilical cord blood and amniotic fluid in both term and preterm pregnancies.

In 2014, the first in-depth characterization in a population-based cohort of the human placental microbiota was presented. It is mainly composed of nonpathogenic commensal microbiota (from phyla *Firmicutes, Proteobacteria, Bacteroidetes*, *Fusobacteria,* and *Tenericutes*), is metabolically active and resembles the oral microbiota from non-pregnant subjects [32]. In addition, the microbiota composition is associated with antenatal infection and preterm birth [32] but whether the bacteria are causal is not clear. The placental microbiota is altered in chorioamnionitis [33], excess gestational weight gain [34] and low birth weight in full-term neonates [35]. While most of placental studies are focused on an adverse role of the bacteria, microbial presence may be beneficial for both mother and baby. It can induce endotoxin tolerance in the fetus, promote tolerance to beneficial commensal bacteria and colonize the fetal gut and optimize nutrition [36]. However, the methods of sample collection and the low-bacterial abundance call for caution and rigorous non-template controls when interpreting PCR-based and metagenomic results, as even a minimal source of contamination can significantly impact microbiome profiles.

Mother's Microbial Heritage—How Does the Maternal Microbiota Impact the Microbiota of the Infant?

Microbiota composition can be vertically transmitted from parent to offspring (see Fig. 22.2): Specific probiotic strains consumed by the mother during pregnancy have later been isolated from the feces of

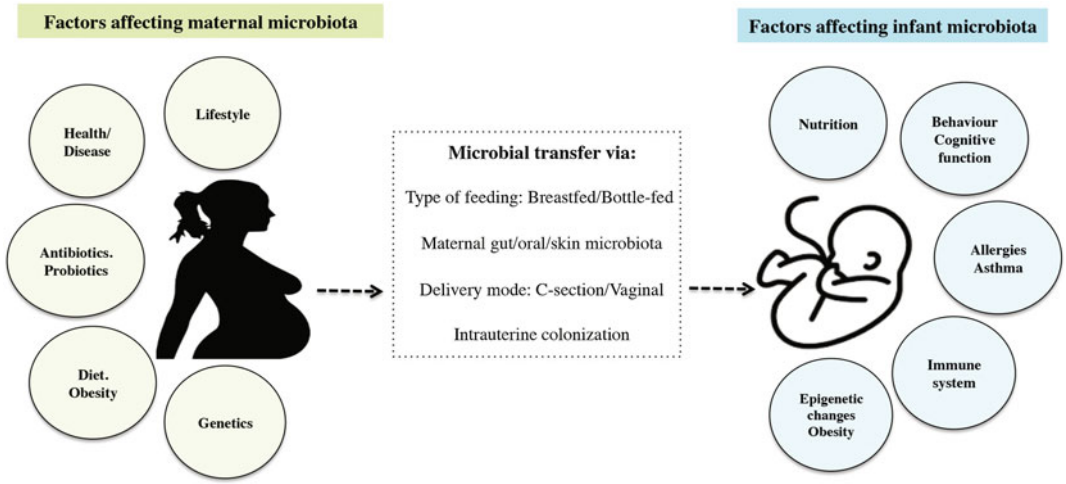


Fig. 22.2 Factors determining microbiota composition in mother and infant. *Legend* Important determinants of maternal (*left* section of figure, in Title: *green*) and infant (*right* section of figure, in *blue*) are listed. Factors affecting the transfer of bacteria from mother to baby in the perinatal period are listed in the middle section of the figure

neonates confirming the vertical transmission of the mother's microbiota to the infant [37]. The mode of delivery is a determinant of the vertical transmission of bacteria affecting the infant's health from birth to adulthood [26]. Babies born vaginally are mainly colonized by the vaginal microbiota (*Lactobacillus, Prevotella* and *Sneathia* spp), whereas babies born by Cesarean section are firstly colonized by bacteria from maternal skin (*Staphylococcus, Corynebacterium,* and *Propionibacterium* spp) and from the hospital environment (*Clostridium difficile, Staphylococci*) [38]. Cesarean section is also associated with lower bacterial diversity and lower abundance of *Bifidobacterium* spp, *Lactobacillus* spp, and *Bacteroides* spp [39]. Vaginal microbial transfer has been proposed as a novel strategy for restoring the microbiota of babies born by Cesarean section [40]. The implications of this strategy have yet to be explored in larger cohorts and beyond the first month of life. Cesarean section and high counts of *C. difficile* have been associated with infantile allergy and asthma, indicating that there may be an association of gut bacteria with the neonatal immune system [39].

Breastfeeding also is a source of continuous bacterial inoculation from mother to baby. Breast-fed infants have higher abundance of *Bacteroides*, *Prevotella,* and *Bifidobacterium*, with formula-fed infants having a higher prevalence of *C. difficile* [41]. Breastfeeding is linked to a lower risk of infancy and adult obesity [42], which may be partially due to differences in microbial colonization. A child's energy storage potential may be shifted by inappropriate colonization with microbes possessing the capacities to extract more energy from food [41]. In fact, a longitudinal study found that overweight children had fewer *Bifidobacteria* as infants than their normal-weight counterparts [43].

Maternal obesity is another major factor predicting the infant's microbiome. High maternal BMI is linked with lower levels of important immunomodulators in breastmilk and fewer *Bifidobacteria*, which could affect the later health of the infant [44]. Moreover, babies born from mothers with type 2 diabetes, maternal eczema, or respiratory problems have altered microbiota composition [45, 46]. Antibiotic use and water birth can also modulate the newborn's microbiome although these will not be addressed further.

Probiotics

Definitions and Traits

The generally accepted definition of probiotics is live microorganisms that, when provided in adequate amounts, confer a health benefit for the host. Probiotics have been used not only in humans but also to promote health in (farm) animals.

The genus of *Lactobacilli* is commonly used as a probiotic strain. *Lactobacilli* have a number of different functions in the human gastrointestinal tract ranging from direct bactericidal effects on surrounding bacteria, protecting the gastrointestinal barrier, reducing energy substrate availability as well as changing the host's inflammatory response [47]. These actions are partially achieved by *Lactobacillus* itself, e.g., through production of lactic acid and hydrogen peroxide and partially through interaction with the host, e.g., through activation of immune cells in Peyer's patches, changing Toll-like receptor expression or by increasing mucus production from goblet cells [47]. The widely used probiotic strain *Lactobacillus rhamnosus* GG uses its extracellular pili—hair-like appendages on the surface of the bacteria—to interact with the host [48]. In healthy adults, daily supplementation with *L. rhamnosus* GG for 3 weeks does not alter the overall gut microbiota composition [49] even though its abundance in the gut microbiota significantly increases during supplementation but disappears after completing the study [49]. Whether or not supplementation with *L. rhamnosus* GG can alter the overall composition after illness or antibiotic treatment in humans is not known.

Bifidobacterium animalis subspecies *lactis* is another strain of bacteria commonly used as a probiotic strain especially since it relatively impervious to changes in oxygen availability and (stomach) acid [50]. *B. lactis* BB-12 supplementation has been shown to prevent diarrhea, treat atopic eczema in infants, and to maintain a balanced gut microbiota [50]. Supplementation of human volunteers with a yogurt drink with *B. lactis* BB-12, showed that the bacteria could be detected in stool of 70% of the volunteers during active supplementation but no longer after 2 weeks' cessation [50]. The bacteria were found to be alive in 80% of the stool samples that showed bacteria by PCR, indicating that they survive gastrointestinal transit [50].

Some studies use combinations of different probiotic strains to induce an effect. Monozygotic female twins consumed a fermented milk product with five different probiotic strains (three *Lactobacilli* species, one *Bifidobacterium,* and one *Streptococcus* strain) for seven weeks, which did not change their overall microbiome composition or which genes the bacteria expressed [51]. This study confirmed that the gut microbiota composition within an individual is relatively consistent over time. The species present in the fermented milk product were detectable for the duration of the supplementation but became undetectable within 2 weeks after cessation of the fermented milk product [51].

The specific effects of probiotics are strain or substrain-specific and in general, there are no major changes to the composition of the overall gut microbiota in response to probiotic supplementation. Furthermore, it appears that the supplemented bacteria do not become permanent constituents of the gut microbiota since their abundance decreases rapidly after ceasing supplementation (Fig. 22.3).

Probiotics to Prevent GDM

There are a small number of studies that have investigated the effects of probiotics in the prevention of GDM [52].

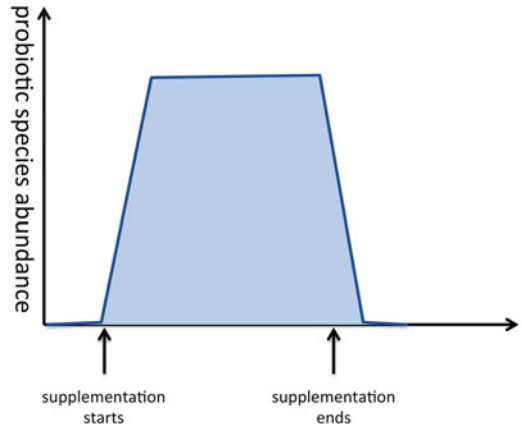


Fig. 22.3 Probiotics species abundance in gut microbiome. *Legend* This graph shows how the abundance of the probiotic species changes over the course of the supplementation. The abundance rapidly increases after the start of the intervention (*first arrow*) and decreases rapidly (within days to weeks) after supplementation ceases (*second arrow*)

Observational Studies

There is only one observational supplementation study in a community healthcare setting where pregnant women received a combination of probiotics *Lactobacillus plantarum, Lactobacillus salivarius, Bifidobacterium lectis,* and *Streptococcus thermophilus* in addition to vitamin supplementation. This supplementation strategy together with lifestyle counseling lowered the risk of GDM as compared to patients who were not supplemented [53].

Randomized Controlled Trials (RCTs) to Prevent GDM

A recent meta-analysis of RCTs of nutritional manipulation to prevent GDM indicated that supplementation with probiotics decreases the incidence of GDM by 60% [54]. The first RCT in this area, which included 256 women, reported a 66% reduction in GDM for women receiving *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB-12 and dietary counseling compared with those receiving the placebo with dietary counseling or receiving placebo without dietary counseling from early pregnancy onward [55]. The SPRING study, an RCT aiming to enroll 540 high-risk overweight and obese women using the same probiotic supplements has finished recruitment and is expected to report their outcome at the end of 2016 [56]. A second RCT of 70 women used a yogurt supplemented with *Lactobacillus acidophilus* LA5 and *Bifidobacterium animalis* BB-12 for a 9 week period. Women receiving the probiotics had a lower increase in insulin levels and HOMA-IR scores across the third trimester [57]. In contrast, an RCT of 138 women with obesity in pregnancy randomized to 4 weeks of placebo or a probiotic capsule containing *Lactobacillus salivarius* UCC118 between 24 and 28 weeks gestation, showed no difference in fasting glucose, GDM or infant birth weight [58]. These results indicate that the timing and duration of the intervention as well as the strains used may be crucial in determining their success.

Randomized Controlled Trials (RCTs) to Treat GDM

Probiotic supplementation has also been assessed as a treatment for GDM (Fig. 22.4). One RCT randomized 149 women with GDM to *Lactobacillus salivarius* UCC118 or placebo from their

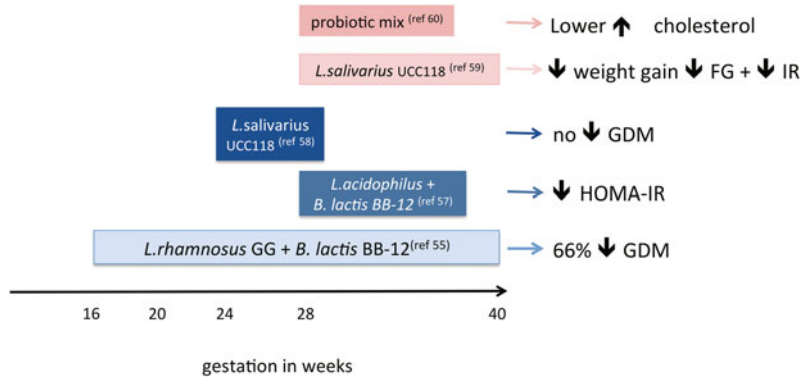


Fig. 22.4 RCTs of probiotics intervention in pregnancy targeting GDM. *Legend* Probiotic interventions to prevent GDM (in *blue*) and in GDM (in *pink*). The length of the box indicates the length of the supplementation. The bacterial strains used are indicated, the probiotic mix included: *Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, and *Lactobacillus delbrueckii bulgaricus* LBY-27. FG, fasting glucose; IR, insulin resistance; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model of assessment-insulin resistance

diagnosis until delivery [59]. Probiotic supplementation did not change glycemic control, the need for pharmacological therapy, or infant birth weight but attenuated the rise in total and LDL cholesterol in late gestation. Another RCT assigned a combination of *Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, and *Lactobacillus delbrueckii bulgaricus* LBY-27 or placebo to 64 women with GDM from diagnosis for 8 weeks. Probiotic supplementation resulted in a lower weight gain in the last 2 weeks of the study alone, a greater decrease in fasting glucose and lower insulin resistance [60]. While these studies indicate that reversing GDM with probiotics may not be feasible, they point toward beneficial effects in lowering metabolic abnormalities.

Prebiotics/Synbiotics

Oligosaccharides, such as fructooligosaccharides, galactooligosaccharides, and lactulose are often used as prebiotics [61]. Prebiotics serve as a food source for the bacteria of the gut microbiota and can thereby improve the health of the host. In synbiotic products, a mixture of probiotics and prebiotics are used which is assumed to improve the survival of the probiotic strains and thereby have an added benefit over probiotics alone. Synbiotic supplementation increases the presence of ketones and SCFA in the feces, indicating that gut metabolic activity may be altered and more anti-inflammatory stimuli are provided [61]. Supplementation of pregnant women in their third trimester with a synbiotic (*L. sporogenes* and inulin), showed lower increases in fasting insulin and its associated indices (HOMA-IR and HOMA-B) but no effects on fasting plasma glucose or serum hs-CRP levels [62]. The synbiotic supplementation also reduced serum triglycerides and VLDL levels [63] in these women. These results indicate the need for more studies into the benefits of prebiotics and/or synbiotics for prevention of pregnancy complications.

Recommendations and Guidelines

The gut and vaginal microbiota change in pregnancy and the placenta develops its own microbiota. Transfer of maternal bacteria to the baby occurs prenatally, perinatally and continues postnatally with skin contact and breastfeeding. Probiotics have the potential to alter pregnancy outcomes through altering the function of the microbiome thereby affecting metabolism and/or inflammatory processes.

While no adverse effects have been reported of probiotics use, there is currently no definitive evidence supporting the use of specific probiotic strains to prevent gestational diabetes mellitus. However, there are indications that starting an intervention with probiotic mixtures of multiple strains in early second trimester could prevent gestational diabetes mellitus.

In women who have developed gestational diabetes mellitus, probiotic interventions could serve to improve metabolic markers including insulin resistance and circulating lipids. Again, mixtures of probiotic strains including *Lactobacillus* species appear more effective.

Finally, it is not clear if the addition of prebiotic compounds such as insulin can improve the efficacy of probiotics and this should be investigated further. Since many prebiotics increase the amount of indigestible carbohydrates, which can also be achieved by increasing dietary fiber intake, dietary advice emphasizing the importance of dietary fiber in pregnant women is paramount.

Conclusions

In pregnancy, there are major changes to the gut microbiota. These changes contribute to the metabolic changes of pregnancy. Dysbiosis is associated with adverse pregnancy outcomes. Manipulation of the gut microbiota by probiotic, prebiotic, or synbiotic supplementation could improve pregnancy outcomes. There is some evidence that probiotic supplementation, when administered from early in pregnancy and for a prolonged period, can prevent the development of GDM. More research is necessary but supplementation would provide an easily implementable and cheap means of preventing GDM, should this be shown to be an effective strategy.

References

1. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59–65.
2. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. bioRxiv. 2016.
3. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011;473(7346):174–80.
4. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev. 2010;90 (3):859–904.
5. Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. Expert Review of Anti-infective Therapy. 2010;8(4):435–54.
6. Gomez de Aguero M, Ganal-Vonarburg SC, Fuhrer T, Rupp S, Uchimura Y, Li H, et al. The maternal microbiota drives early postnatal innate immune development. Science. 2016;351(6279):1296–302.
7. Collado MC, Isolauri E, Laitinen K, Salminen S. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. Am J Clin Nutr. 2008;88(4):894–9.
8. Koren O, Goodrich Julia K, Cullender Tyler C, Spor A, Laitinen K, Kling Bäckhed H, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell. 2012;150(3):470–80.
9. Jost T, Lacroix C, Braegger C, Chassard C. Stability of the maternal gut microbiota during late pregnancy and early lactation. Curr Microbiol. 2014;68(4):419–27.

10. Mukhopadhya I, Hansen R, El-Omar EM, Hold GL. IBD-what role do Proteobacteria play? Nat Rev Gastroenterol Hepatol. 2012;9(4):219–30.
11. Avershina E, Storrø O, Øien T, Johnsen R, Pope P, Rudi K. Major faecal microbiota shifts in composition and diversity with age in a geographically restricted cohort of mothers and their children. FEMS Microbiol Ecol. 2014;87(1):280–90.
12. Gohir W, Ratcliffe EM, Sloboda DM. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pediatr Res. 2015;77(1–2):196–204.
13. Santacruz A, Collado MC, Garcia-Valdes L, Segura MT, Martin-Lagos JA, Anjos T, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 2010;104(1):83–92.
14. Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri JM, Moreno LA, et al. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. Int J Obes (Lond). 2009;33(7):758–67.
15. Priyadarshini M, Thomas A, Reisetter AC, Scholtens DM, Wolever TM, Josefson JL, et al. Maternal short-chain fatty acids are associated with metabolic parameters in mothers and newborns. Transl Res. 2014;164(2):153–7.
16. Voltolini C, Battersby S, Etherington SL, Petraglia F, Norman JE, Jabbour HN. A novel antiinflammatory role for the short-chain fatty acids in human labor. Endocrinology. 2012;153(1):395–403.
17. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS ONE. 2010;5(2):e9085.
18. Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143 (4):913–6.e7.
19. Fugmann M, Breier M, Rottenkolber M, Banning F, Ferrari U, Sacco V, et al. The stool microbiota of insulin resistant women with recent gestational diabetes, a high risk group for type 2 diabetes. Sci Rep. 2015;5:13212.
20. Aagaard K, Riehle K, Ma J, Segata N, Mistretta T-A, Coarfa C, et al. A Metagenomic Approach to Characterization of the Vaginal Microbiome Signature in Pregnancy. PLoS ONE. 2012;7(6):e36466.
21. DiGiulio DB, Callahan BJ, McMurdie PJ, Costello EK, Lyell DJ, Robaczewska A, et al. Temporal and spatial variation of the human microbiota during pregnancy. 2015;112(35):11060–5.
22. Romero R, Hassan SS, Gajer P, Tarca AL, Fadrosh DW, Nikita L, et al. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. Microbiome. 2014;2(1):4.
23. Leitich H, Bodner-Adler B, Brunbauer M, Kaider A, Egarter C, Husslein P. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. Am J Obstet Gynecol. 2003;189(1):139–47.
24. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human oral microbiome. J Bacteriol. 2010;192(19):5002–17.
25. Wade WG. The oral microbiome in health and disease. Pharmacol Res. 2013;69(1):137–43.
26. Solt I. The human microbiome and the great obstetrical syndromes: a new frontier in maternal-fetal medicine. Best Pract Res Clin Obstet Gynaecol. 2014.
27. Konopka T, Paradowska-Stolarz A. Periodontitis and risk of preterm birth and low birthweight–a meta-analysis. Ginekol Pol. 2012;83(6):446–53.
28. Boggess KA, Lieff S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol. 2003;101(2):227–31.
29. Koren O, Spor A, Felin J, Fak F, Stombaugh J, Tremaroli V, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc Natl Acad Sci U S A. 2011;15(108 Suppl 1):4592–8.
30. Shillitoe E, Weinstock R, Kim T, Simon H, Planer J, Noonan S, et al. The oral microflora in obesity and type-2 diabetes. J Oral Microbiol. 2012;4.
31. Satokari R, Gronroos T, Laitinen K, Salminen S, Isolauri E. Bifidobacterium and Lactobacillus DNA in the human placenta. Lett Appl Microbiol. 2009;48(1):8–12.
32. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Science translational medicine. 2014 May 21;6(237):237ra65.
33. Prince AL, Ma J, Kannan PS, Alvarez M, Gisslen T, Harris RA, et al. The placental microbiome is altered among subjects with spontaneous preterm birth with and without chorioamnionitis. Am J Obstet Gynecol. 2016.
34. Antony KM, Ma J, Mitchell KB, Racusin DA, Versalovic J, Aagaard K. The preterm placental microbiome varies in association with excess maternal gestational weight gain. Am J Obstet Gynecol. 2015;212(5):653.e1–16.
35. Zheng J, Xiao X, Zhang Q, Mao L, Yu M, Xu J. The placental microbiome varies in association with low birth weight in full-term neonates. Nutrients. 2015;7(8):6924–37.
36. Sisti G, Kanninen TT, Witkin SS. Maternal immunity and pregnancy outcome: focus on preconception and autophagy. Genes Immun. 2016;17(1):1–7.
37. Schultz M, Gottl C, Young RJ, Iwen P, Vanderhoof JA. Administration of oral probiotic bacteria to pregnant women causes temporary infantile colonization. J Pediatr Gastroenterol Nutr. 2004;38(3):293–7.

38. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971–5.
39. Prince AL, Antony KM, Ma J, Aagaard KM. The microbiome and development: a mother's perspective. Semin Reprod Med. 2014;32(1):14–22.
40. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. 2016;22(3):250–3.
41. Madan JC, Farzan SF, Hibberd PL, Karagas MR. Normal neonatal microbiome variation in relation to environmental factors, infection and allergy. Curr Opin Pediatr. 2012;24(6):753–9.
42. Thompson AL. Developmental origins of obesity: early feeding environments, infant growth, and the intestinal microbiome. Am J Hum Biol. 2012;24(3):350–60.
43. Luoto R, Kalliomaki M, Laitinen K, Delzenne NM, Cani PD, Salminen S, et al. Initial dietary and microbiological environments deviate in normal-weight compared to overweight children at 10 years of age. J Pediatr Gastroenterol Nutr. 2011;52(1):90–5.
44. Collado MC, Laitinen K, Salminen S, Isolauri E. Maternal weight and excessive weight gain during pregnancy modify the immunomodulatory potential of breast milk. Pediatr Res. 2012;72(1):77–85.
45. Hu J, Nomura Y, Bashir A, Fernandez-Hernandez H, Itzkowitz S, Pei Z, et al. Diversified microbiota of meconium is affected by maternal diabetes status. PLoS ONE. 2013;8(11):e78257.
46. Gosalbes MJ, Llop S, Valles Y, Moya A, Ballester F, Francino MP. Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin Exp Allergy. 2013;43(2):198–211.
47. Griffin C. Probiotics in obstetrics and gynaecology. Aust N Z J Obstet Gynaecol. 2015;55(3):201–9.
48. Kankainen M, Paulin L, Tynkkynen S, von Ossowski I, Reunanen J, Partanen P, et al. Comparative genomic analysis of Lactobacillus rhamnosus GG reveals pili containing a human-mucus binding protein. Proc Natl Acad Sci. 2009;106(40):17193–8.
49. Lahti L, Salonen A, Kekkonen RA, Salojarvi J, Jalanka-Tuovinen J, Palva A, et al. Associations between the human intestinal microbiota, *Lactobacillus rhamnosus* GG and serum lipids indicated by integrated analysis of high-throughput profiling data. PeerJ. 2013;1:e32.
50. Palaria A, Johnson-Kanda I, O'Sullivan DJ. Effect of a synbiotic yogurt on levels of fecal bifidobacteria, clostridia, and enterobacteria. Appl Environ Microbiol. 2012;78(4):933–40.
51. McNulty NP, Yatsunenko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, et al. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Sci Trans Med. 2011;3(106):106ra-ra.
52. Barrett Helen L, Dekker Nitert M, Conwell Louise S, Callaway Leonie K. Probiotics for preventing gestational diabetes. Cochrane Database of Systematic Reviews [serial on the Internet]. 2012;(7): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD009951/frame.html
53. Stone LP, Stone PM, Rydbom EA, Stone LA, Stone TE, Wilkens LE, et al. Customized nutritional enhancement for pregnant women appears to lower incidence of certain common maternal and neonatal complications: an observational study. Glob Adv Health Med. 2014;3(6):50–5.
54. Rogozinska E, Chamillard M, Hitman GA, Khan KS, Thangaratinam S. Nutritional manipulation for the primary prevention of gestational diabetes mellitus: a meta-analysis of randomised studies. PLoS ONE. 2015;10(2):e0115526.
55. Laitinen K, Poussa T, Isolauri E. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr. 2009;101(11):1679–87.
56. Nitert MD, Barrett HL, Foxcroft K, Tremellen A, Wilkinson S, Lingwood B, et al. SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. BMC Pregnancy Childbirth. 2013;13:50.
57. Asemi Z, Samimi M, Tabassi Z, Naghibi Rad M, Rahimi Foroushani A, Khorammian H, et al. Effect of daily consumption of probiotic yoghurt on insulin resistance in pregnant women: a randomized controlled trial. Eur J Clin Nutr. 2013;67(1):71–4.
58. Lindsay KL, Kennelly M, Culliton M, Smith T, Maguire OC, Shanahan F, et al. Probiotics in obese pregnancy do not reduce maternal fasting glucose: a double-blind, placebo-controlled, randomized trial (Probiotics in Pregnancy Study). Am J Clin Nutr. 2014;99(6):1432–9.
59. Lindsay KL, Brennan L, Kennelly MA, Maguire OC, Smith T, Curran S, et al. Impact of probiotics in women with gestational diabetes mellitus on metabolic health: a randomized controlled trial. Am J Obstet Gynecol. 2015;212(4):496.e1–11.
60. Dolatkhah N, Hajifaraji M, Abbasalizadeh F, Aghamohammadzadeh N, Mehrabi Y. Mesgari Abbasi M. Is there a value for probiotic supplements in gestational diabetes mellitus? A randomized clinical trial. J Health Popul Nutr. 2015;33(1):25.

61. Vitali B, Ndagijimana M, Cruciani F, Carnevali P, Candela M, Guerzoni EM, et al. Impact of a synbiotic food on the gut microbial ecology and metabolic profiles. BMC Microbiol. 2010;10(1):1–13.
62. Taghizadeh M, Asemi Z. Effects of synbiotic food consumption on glycemic status and serum hs-CRP in pregnant women: a randomized controlled clinical trial. Hormones. 2014;13(3):398–406.
63. Taghizadeh M, Hashemi T, Shakeri H, Abedi F, Sabihi SS, Alizadeh SA, et al. Synbiotic food consumption reduces levels of triacylglycerols and VLDL, but not cholesterol, LDL, or HDL in plasma from pregnant women. Lipids. 2014;49(2):155–61.

Chapter 23
The Role of Exercise in the Management of Gestational Diabetes Mellitus

Kym J. Guelfi, Rhiannon E. Halse and John P. Newnham

Key Points

- There is accumulating evidence that regular exercise benefits glycaemic control in GDM pregnancies.
- Regular exercise may also provide benefits that conventional treatment of GDM via nutrition or pharmacologic therapy alone cannot, such as enhanced maternal fitness and psychological well-being.
- Despite these potential benefits, most women are insufficiently active during pregnancy and regular structured exercise is not part of routine antenatal diabetic care in most parts of the world.
- Whether exercise can prevent GDM is still not clear.
- More research is needed to allow for the development of evidence-based guidelines regarding the optimum exercise prescription for women diagnosed with GDM.

Keywords Exercise · Physical activity · Gestational diabetes · Inactivity · Recommendations

Abbreviations

Bpm	Beats per minute
BMI	Body mass index
GDM	Gestational diabetes mellitus
HbA1c	Glycated haemoglobin
HRR	Heart rate reserve
$\dot{V}O_2max$	Maximal volume of oxygen consumption
OGTT	Oral glucose tolerance test

K.J. Guelfi (✉)
School of Sport Science, Exercise and Health, The University of Western Australia,
35 Stirling Highway, Crawley, Perth, WA 6009, Australia
e-mail: kym.guelfi@uwa.edu.au

R.E. Halse
School of Nutrition, Dietetics and Food Technology, Curtin University,
Kent Street, Bentley, Perth, WA 6102, Australia
e-mail: rhiannon.halse@curtin.edu.au

J.P. Newnham
School of Women's and Infants' Health, The University of Western Australia,
35 Stirling Highway, Crawley, Perth, WA 6009, Australia
e-mail: john.newnham@uwa.edu.au

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_23

Introduction

Historically, pregnant women have been discouraged from exercise, mainly due to social and cultural biases relating to speculative concerns about safety for the fetus, rather than the results of scientific investigation. Today, the benefits of regular exercise during pregnancy are well established. In particular, regular exercise plays an important role in the management, and potentially also prevention, of gestational diabetes mellitus (GDM). Yet, most women are insufficiently active during pregnancy and regular structured exercise is not part of routine antenatal diabetic care in most parts of the world. Furthermore, evidence-based guidelines regarding the optimum exercise prescription for women diagnosed with GDM are lacking. Although ongoing research is required, this chapter outlines the benefits of regular exercise during pregnancy, with a specific focus on women diagnosed with GDM, together with current recommendations and special considerations for exercise prescription during pregnancy.

The Benefits of Exercise During Pregnancy

There is currently no evidence to suggest that participation in regular exercise during an uncomplicated pregnancy is detrimental to the woman or to her fetus [1]. Rather, there are many benefits to be gained from the performance of regular exercise during pregnancy. These benefits include enhanced cardiovascular fitness and the prevention of excessive weight gain for the woman, as well as psychological benefits related to body image, perceived health status and reduced symptoms of depression [1–5]. There is also some evidence to suggest that regular exercise during pregnancy is associated with shorter and less complicated labour, together with fewer neonatal complications [6, 7], although research is limited and not conclusive. The benefits of regular exercise during pregnancy also appear to extend to the offspring, with animal studies demonstrating favourable effects on glucose tolerance, insulin sensitivity and body composition [8], while studies in humans are limited to some evidence of beneficial effects of maternal exercise for infant cardiac autonomic control [9].

The Benefits of Exercise During Pregnancy Complicated by GDM

In addition to the previously mentioned benefits of regular exercise during pregnancy, maternal exercise appears to play an important role in the management of pregnancies complicated by GDM (Table 23.1). In particular, exercise can assist with maintaining blood glucose concentrations within the appropriate range. This blood glucose-lowering effect of exercise in women with GDM has been demonstrated both acutely and in response to regular exercise participation.

Table 23.1 Potential benefits of regular exercise during a pregnancy complicated by GDM

• Acute lowering of blood glucose concentrations
• Reduced HbA1c
• Reduced fasting and postprandial glucose responses
• Reduced requirement for insulin therapy
• Increased maternal cardiovascular fitness
• Enhanced psychological well-being
• Reduced risk of GDM-related macrosomia and caesarean delivery

Acutely, a single session of exercise consisting of 30 min of stationary cycling has been shown to lower blood glucose concentrations in women with GDM, with moderate intensity exercise (55% of maximal aerobic capacity [$\dot{V}O_2$max]) more effective than low intensity exercise (35% $\dot{V}O_2$max) [10]. Similarly, Davenport et al. [11] reported an average 2.0 mmol/l decline in capillary glucose concentrations in response to low intensity walking bouts, while Halse et al. [12] showed a mean pre- to post-exercise (stationary cycling) decline in capillary glucose concentrations from 6.3 ± 0.8 to 4.9 ± 0.7 mmol/l in women diagnosed with GDM. Furthermore, Garcia-Patterson and colleagues [13] reported that 1 h of postprandial self-paced walking attenuated the post-meal glucose excursion in women with GDM compared with a resting (no exercise) control condition. These acute effects of exercise on glycaemia are likely attributed to the increased rate of whole body glucose disposal in response to exercise. This is due to enhanced recruitment of intracellular glucose transporters, exercise-induced increases in blood flow and resultant insulin delivery, as well as enhancement of skeletal muscle sensitivity to insulin [14]. However, it must be noted that not all studies have reported benefits of an acute bout of exercise for glycaemia in women with GDM [15], hence further investigation of the potential glucose-lowering effect of a single bout of exercise in women diagnosed with GDM is warranted.

With respect to regular exercise, there is evidence to suggest benefits for both fasting and postprandial glycaemic responses, together with daily capillary glucose concentrations and glycated haemoglobin (HbA1c). For instance, Jovanovic-Peterson and colleagues [16] reported a reduction in HbA1c, fasting and postprandial glucose concentrations in response to a 50 g glucose load following a 6 week exercise programme consisting of 3 × 20 min sessions per week of arm ergometry at <50% $\dot{V}O_2$max commenced at 28 weeks of pregnancy in women with GDM, compared with GDM women treated with diet therapy alone. Davenport et al. [11] observed lower fasting and postprandial glucose concentrations in overweight women in response to a programme of regular walking from GDM diagnosis to delivery (25 min progressing to 40 min at 30% heart rate reserve [HRR] 3 times per week). More recently, Halse et al. [12] reported lowered daily home-monitored postprandial glucose concentrations following 6 weeks of supervised home-based stationary cycling (25 min progressing to 45 min at varying intensities 3 times per week) plus unsupervised aerobic exercise (twice per week) commenced upon diagnosis of GDM, compared with a control group receiving standard care alone. A study using resistance exercise training (30–40 min sessions performed 2–3 times per week) from the time of diagnosis of GDM has also reported improved capillary glucose control compared with a non-exercising control group [17]. However, not all studies have confirmed benefits for glycaemic control in response to regular exercise commenced upon GDM diagnosis. For instance, Avery and colleagues [18] found no effect of a partially home-based exercise programme (2 × 30 min supervised cycle ergometry sessions per week at 70% of age-predicted maximum heart rate, plus two unsupervised sessions of either cycling or walking) commenced from diagnosis of GDM (∼28 weeks of pregnancy) on postprandial blood glucose levels and glycaemic control compared with a standard care alone.

In addition to the growing body of evidence that regular exercise benefits glycaemic control in pregnancies complicated by GDM, there is research to suggest favourable outcomes in relation to the need for pharmacological intervention. Brankston et al. [19] demonstrated reduced requirement for insulin therapy in overweight women with GDM who participated in a programme of regular resistance training from diagnosis (29.3 ± 2.1 weeks of pregnancy) until delivery. The programme consisted of two sets of 15 repetitions progressing to three sets of 20 repetitions of eight different circuit exercises performed three times per week. Although the absolute number of women requiring insulin treatment was similar between groups, the daily dose of insulin required was significantly reduced in women randomised to exercise, along with a delayed time from diagnosis to beginning insulin therapy. When women with a body mass index (BMI) >25 kg/m^2 were considered as a subgroup, those randomised to exercise were less likely to require insulin therapy (30%), compared with the diet alone group (80%). More recently, de Barros and colleagues [17] reported a reduction in

the number of women requiring insulin (irrespective of BMI) following the performance of 30–40 min of resistance exercise performed 2–3 times per week from diagnosis of GDM to delivery. However, no differences in the amount of insulin required or latency to insulin treatment were noted between exercise and control groups in this study. Regular walking has also been shown to reduce the need for insulin requirement in overweight women (decreased daily units and frequency of administration) [11]. However, such benefits are not consistently reported, with Avery and colleagues [18] finding no effect of their partially home-based exercise programme on the incidence of insulin therapy.

Regular exercise for a woman diagnosed with GDM may also provide benefits that conventional treatment via nutrition or pharmacologic therapy alone cannot. In particular, regular exercise commenced upon diagnosis of GDM can increase maternal fitness [18, 20]. While often underappreciated, this is of great importance given the beneficial relationship between cardiovascular fitness during pregnancy and fitness and cardiovascular risk factors later in life [21]. Furthermore, regular exercise may benefit the woman diagnosed with GDM through enhanced psychological well-being. Indeed, regular exercise has been shown to enhance body image, perceived health status and reduce symptoms of depression during pregnancy [1–4], however, research specific to GDM women is lacking. There is also some evidence to suggest that attitudes towards exercise may be improved with as little as 6 weeks of supervised exercise in women diagnosed with GDM [20]. Yet despite these wide-ranging benefits, regular structured exercise is typically not incorporated into routine antenatal diabetic care.

Regarding the effect of regular exercise during a pregnancy complicated by GDM on obstetric and neonatal outcomes, there is a limited research from which to draw conclusions. The previously mentioned study by Halse and colleagues [20] found no difference in the onset, mode, or duration of labour, gestational age at delivery, incidence of preterm birth, and mean neonatal anthropometrics between their exercise training and control group of women with GDM. However, the study was not powered to deduce firm conclusions concerning these outcomes. Meanwhile, Barakat and co-workers [22] reported reduced risk of GDM-related macrosomia and caesarean delivery in women participating in regular moderate-intensity exercise during pregnancy. Clearly, more randomised controlled exercise interventions are needed to determine whether maternal exercise in a pregnancy complicated by GDM does indeed benefit maternal and neonatal obstetric outcomes.

Exercise for the Prevention of GDM

Although there is a growing body of evidence to support a role of regular exercise for the management of GDM, whether exercise can prevent manifestation of the condition in the first place is much less clear. Evidence in support of a role for exercise to prevent GDM comes primarily from epidemiological data indicating reduced risk for GDM with increasing physical activity [23]. In addition, experimental studies have demonstrated favourable effects on glucose tolerance in response to regular exercise during pregnancy [24, 25]. However, the results from recent randomised controlled trials are conflicting. For instance, Barakat et al. [22] and Stafne et al. [26] reported no effect of antenatal exercise interventions consisting of moderate intensity aerobic, strength and flexibility exercises performed 3 times a week for 45–60 min on the incidence of GDM in apparently healthy pregnant women. Likewise, Nobles et al. [27] found no effect of an antenatal exercise intervention commenced at 10–12 weeks of pregnancy that aimed to achieve 30 min of moderate intensity physical activity through self-selected activities on the incidence of GDM in ‘at risk’ women. On the other hand, Cordero et al. [28] observed reduced prevalence of GDM with a programme of land (twice a week) and aquatic-based (once a week) aerobic, strength and flexibility exercises commenced at 10–14 weeks of pregnancy.

The inconsistency between studies may be attributed to a number of factors relating to the timing of the commencement of the intervention, the precise exercise prescription and low exercise compliance. It is also plausible that the factors underlying a woman's risk for GDM are not responsive to a short-term lifestyle intervention commenced during the second and third trimesters of pregnancy. In particular, interventions likely need to be commenced earlier in pregnancy, and possibly even pre-conception, given that placental function and gene expression are programmed by the first trimester of pregnancy [29]. In support of this need for a life-course approach to the prevention of chronic disease and early intervention, our group has recently found in a randomised controlled trial that the risk of GDM in women with a history of the condition in a previous pregnancy was unaltered by a 14 week exercise intervention commenced at 14 weeks of pregnancy; however, the risk of GDM recurrence was significantly influenced by baseline physical activity levels upon entering the study (i.e. before 14 weeks of pregnancy) [30].

Recommendations for Exercise During Pregnancy

The specific nature of guidelines for exercise during pregnancy varies between countries [31]. In general, women are encouraged to participate in aerobic and strength conditioning exercise during pregnancy in the absence of contraindications. In Australia, current physical activity guidelines for adults recommend being active on most, preferably all, days each week [32]. More specifically, individuals should aim to accumulate 150–300 min of moderate intensity physical activity, or 75–150 min of vigorous exercise, or some combination of the two each week. In addition to this, participation in muscle strengthening exercises is recommended at least 2 days per week. Importantly, sedentary behaviour should also be reduced by minimising the amount of time spent in prolonged sitting and breaking up long periods of sitting as often as possible [32]. These guidelines are also relevant for healthy pregnant women. In particular, women should be encouraged to continue their exercise routine during pregnancy in the absence of contraindications, provided some additional considerations are adhered to (as outlined below). For women who have been inactive prior to pregnancy, regular exercise may be introduced slowly within these outlined parameters. For women with obstetric complications, participation in regular exercise may still be suitable following appropriate medical evaluation and modification of the exercise prescription.

At present, there are no evidence-based guidelines for exercise in pregnancy specific to GDM. However, the Fifth International Workshop-Conference on GDM stated that women with the condition should participate in 30 min of planned physical activity each day [33] which is consistent with current guidelines for exercise for the general population. More research is needed to allow for the development of evidence-based guidelines for exercise following a diagnosis of GDM to provide the best outcome for these women and their offspring. As such, the information below reflects the considerations for exercise prescription during pregnancy in general, with some additional points requiring attention for the woman diagnosed with GDM. These recommendations are summarised in Table 23.2.

Table 23.2 General recommendations for exercise during a GDM pregnancy

Frequency	3–5 sessions per week, although daily physical activity would be best
Duration	Aim for at least 30 min each day (accumulate 150–300 min per week)
Intensity	Moderate (should feel "somewhat hard")
Mode	Participate in both aerobic and strength conditioning exercise
Additional	Reduce sedentary behaviour (minimise prolonged sitting)

Pre-exercise Screening

Prior to the commencement of regular exercise in pregnancy, or following a diagnosis of GDM, an assessment of medical and obstetric risks should be undertaken to identify potential contraindications to exercise. One screening tool specific to pregnancy that can assist in this purpose is the PARmed-X for pregnancy [34]. Contraindications to exercise may include cardiovascular disease, poorly controlled asthma, poorly controlled diabetes and bone or joint problems that may be exacerbated by exercise. Contraindications specific to pregnancy include persistent bleeding, placenta praevia, pre-eclampsia, pregnancy-induced hypertension and indicators of increased risk of preterm labour (i.e. incompetent cervix, multiple pregnancy, ruptured membranes, pre-term contractions) [34]. Given that scientific evidence regarding the risks of exercise for women with these conditions is not currently available, exercise prescription for these patients would be unwise. Other potential contraindications to exercise during pregnancy include intrauterine growth restriction, poorly controlled thyroid disease and anaemia. Under these circumstances, assessment of the individual case is required to determine whether exercise prescription is appropriate. For a previously inactive woman diagnosed with GDM, exercise should be introduced slowly, and progression monitored closely.

Exercise Prescription During Pregnancy

Frequency of Exercise

Women should aim to be physically active on most, preferably all days of the week during pregnancy. Daily exercise is likely of particular importance to the woman diagnosed with GDM, although many studies have shown benefit for daily glucose control [11, 12, 16] and the need for insulin therapy [11, 17, 19] with 3–5 sessions per week. Accordingly, women who are previously unaccustomed to exercise may be prescribed a reduced frequency of exercise at the commencement of a programme (i.e. 3 days per week on non-consecutive days).

Duration of Exercise

Women should aim to accumulate 150–300 min of moderate intensity physical activity each week, ideally, through daily participation. For women with GDM, 30 min of planned exercise each day has been recommended [33]. Women who are previously unaccustomed to regular exercise may commence with a shorter duration of exercise (15–20 min), with the aim of slowly progressing to 30 min each day. Previous research showing benefits of regular exercise for women diagnosed with GDM has employed exercise durations ranging from 20 to 25 min at the commencement of a programme, progressing to 40–45 min after a number of weeks [11, 12]. There is currently no evidence-based upper limit for the duration of exercise in pregnancy; however, it is not recommended to extend the duration of exercise beyond 60 min during pregnancy, mainly due to concerns relating to thermoregulation.

Intensity of Exercise

The appropriate intensity of exercise during pregnancy depends on a number of individual characteristics of the women, including her baseline level of fitness, previous exercise experience and

pregnancy-specific symptoms including nausea and fatigue. In general, maintaining a 'moderate' intensity of exercise during pregnancy is adequate to obtain benefits for health, fitness and psychological well-being. However, it should be acknowledged that there is limited research regarding maternal exercise at higher intensities and accordingly, no evidence-based safe upper limit for the intensity of exercise during pregnancy has been established.

The intensity of exercise is most commonly monitored using the heart rate response to exercise and/or ratings of perceived exertion during pregnancy. With respect to the former, heart rate zones equivalent to 60–80% of maximal aerobic capacity have been recommended during pregnancy, with values adjusted based on the fitness levels and BMI [34]. For women younger than 20 years of age, this equates to a heart rate range of 140–155 bpm. For normal weight women between the ages of 20–29, this equates to a heart range of 129–144 bpm (for those with low fitness), 135–150 bpm (for those who are recreationally active) or 145–160 bpm (for those who are fit). For normal weight women between the ages of 30–39, this equates to a heart range of 128–144 bpm (for those with low fitness), 130–145 bpm (for those who are recreationally active), or 140–156 bpm (for those who are fit) [34]. These heart rate zones are adjusted for previously inactive overweight or obese women with lower fitness levels; 102–124 bpm (for those aged 20–29 years) and 101–120 bpm (for those aged 30–39 years) [35]. When monitoring intensity based on the ratings of perceived exertion [36], exercise of moderate intensity is generally achieved when the woman feels like she is working "somewhat hard" (a rating of between 12 and 14 on the 6–20 scale).

Previous research demonstrating benefits for glucose control, the need for insulin therapy and maternal fitness in women diagnosed with GDM have employed exercise of both low and moderate intensities [11, 12, 16]. However, the precise intensity of exercise most advantageous for a woman diagnosed with GDM is unclear, as studies directly comparing different intensities in the literature are limited. Avery and Walker [10] found 30 min of stationary cycling at a moderate intensity exercise (55% $\dot{V}O_2$max) more effective than low intensity exercise (35% $\dot{V}O_2$max) for acutely lowering blood glucose levels in women with GDM. On the other hand, Ruchat et al. [37] reported significant benefits for maternal capillary glucose concentrations in women at high risk of GDM in response to a regular walking programme at either low (30% HRR) or vigorous (70% HRR) intensity commenced at 16–20 weeks of pregnancy. However, the degree of benefit was dependent on the duration of exercise, with these researchers concluding that low intensity exercise may be preferable to vigorous exercise for acutely decreasing capillary glucose concentrations in women at risk of GDM when the duration of exercise is extended beyond 25 min. Clearly, more research is needed to confirm the optimum intensity and duration of exercise for women diagnosed with GDM. In the meantime, it appears sensible for a previously inactive woman diagnosed with GDM to start at a lower intensity and progress slowly with close monitoring.

Mode of Exercise

In the absence of contraindications to exercise, women should be encouraged to participate in both aerobic and strength conditioning exercise throughout pregnancy. Common modes of aerobic exercise during pregnancy include walking, stationary cycling and swimming. Walking is often the most practical mode of exercise during pregnancy, although some women may find the weight-supported nature of stationary cycling and swimming more comfortable in the latter stages of pregnancy. In particular, swimming and other water-based activities may assist with keeping cool during exercise (provided that the water temperature is appropriate) and assisting with oedema due to the redistribution of extravascular fluid with immersion [38]. With respect to running during pregnancy, there is a lack of scientific study, however, it is likely unwise for women not previous accustomed to regular running to commence running-based training during pregnancy. Women who are well accustomed to

running may continue during pregnancy in consultation with their antenatal carer, provided they listen closely to their body and monitor intensity appropriately.

With specific respect to GDM, studies have reported benefits for maternal fitness and glycaemic control with a range of exercise modes including walking, stationary cycling and arm ergometry. No studies have directly compared different training modalities in women diagnosed with GDM; however, Halse et al. [39] reported that women self-select to work at a higher intensity during stationary cycling compared with walking in late pregnancy and this in turn is associated with a greater attenuation of postprandial glucose concentrations. The higher energy expenditure per unit of time associated with self-paced stationary cycling compared with walking is likely attributed to a combination of both the weight-supported nature of cycling and the limited intensity that can be achieved through walking. Regardless, the optimal mode of exercise for a woman diagnosed with GDM is perhaps best informed by the woman's personal preference and enjoyment, provided that the guidelines are adhered to.

In addition to aerobic exercise, muscular conditioning is an important component of a well-rounded exercise programme. General guidelines suggest that women aim for two sessions of strengthening exercises per week, on non-consecutive days, covering the major muscle groups of the body. For each muscle group, women should aim to perform 1–2 sets of 12–15 repetitions with resistance applied in the form of light weights, body weight or elasticised resistance bands. Studies employing resistance exercise within these parameters to women diagnosed with GDM have reported benefits for both glycaemic control and the need for insulin therapy [17, 19]. Sensible precautions for the pregnant woman include performing slow and steady movements, avoiding heavy lifting, and activities that involve straining or holding the breath. In addition, exercises should not be performed lying flat on the back (supine) after the first trimester to prevent the obstruction of venous return by the enlarged uterus, and walking lunges are best avoided to prevent injury to the connective tissue of the pelvis.

Barriers to Exercise in Pregnancy

Despite the well-established benefits of exercise during pregnancy and growing evidence of benefit for the management of GDM, most women do not meet the current recommendations for physical activity participation. This is related, at least in part, to the numerous barriers to exercise participation for the pregnant woman including a lack of time, fatigue, physical discomfort, pregnancy-related nausea and vomiting, and uncertainty about exercise guidelines and how to exercise safely [20, 40, 41]. These barriers are common among pregnant women both with and without GDM [20, 42]. Therefore, the prescription of exercise should include discussion and implementation of strategies to overcome these barriers to exercise during pregnancy. There is some research to suggest that home-based exercise programmes may assist in this regard; however, the inclusion of supervision is likely crucial to ensure appropriate exercise prescription and enhance motivation (Fig. 23.1) [12, 20, 24].

Other Considerations for Exercise During Pregnancy

There are numerous additional considerations for the prescription of exercise during pregnancy. First, it is important to be aware that the increase in body weight as pregnancy progresses is associated with increased loading at the joints, potentially augmenting the risk of injury. Another factor that may contribute to an increased risk of injury is the increase in hormone-induced ligament laxity associated with pregnancy. Accordingly, 'straight-line' weight-supported activities such as water-based exercise

Fig. 23.1 Supervised home-based exercise may assist with overcoming many of the barriers to exercise during pregnancy

or stationary cycling may be preferable compared with weight-bearing exercises involving frequent changes in direction in the later stages of pregnancy. The latter activities may also be important to avoid given that a woman's balance may be compromised due to the altered centre of gravity resulting from the change in weight distribution as pregnancy progresses.

Other physiological changes associated with pregnancy that have implications for exercise prescription include a reduction in blood pressure, an increase in resting and submaximal heart rate and an increase in metabolic rate. To minimise the risk of dizziness or fainting associated with a reduction in blood pressure, the pregnant woman should avoid rapid changes in posture (i.e. moving from lying to standing) and always incorporate a period of warm-up and cool-down with exercise. The elevation in heart rate has implications for monitoring exercise intensity, since lower workloads are required to reach pre-pregnancy target heart rates. For this reason, pregnancy-specific heart rate zones are recommended and best used in combination with ratings of perceived exertion [34]. Regarding the increase in metabolic rate, there is concern about substantial increases in core temperature during exercise increasing the risk of congenital defects in the first trimester. Despite a lack of evidence in humans, it is recommended that the pregnant woman avoid exercising in high temperatures and humidity, ensure adequate hydration and wear loose-fitting clothing.

Additional precautions include avoiding activities with an inherent risk of falling or impact trauma to the abdomen. Activities that involve jumping or bouncing may add extra load to the pelvic floor muscles and are also best avoided. As the uterus grows with advancing pregnancy, the weight of the enlarged uterus may obstruct venous return. For this reason, pregnant women in the second and third trimesters should avoid performing exercises in a supine position for prolonged periods of time. Instead, relevant exercises can be modified to be conducted in a sitting or standing posture.

Table 23.3 Warning signs to stop exercise and seek medical attention

• Pain or tightness in the chest
• Unexplained/unusual shortness of breath
• Dizziness, feeling faint or headache
• Calf pain, swelling or redness
• Acute swelling of ankles, hands or face
• Vaginal bleeding or loss of amniotic fluid
• Decreased movement of the fetus
• Uterine contractions or other potential indicators of pre-term labour (i.e. pain in the lower back, pelvic area or abdomen)

For a pregnant woman diagnosed with GDM, extra precautions include monitoring blood glucose levels pre- and post-exercise. For those requiring insulin, exercise should be scheduled so as not to coincide with peak insulin action, as this may increase the risk of hypoglycaemia. In addition to these special considerations for exercise prescription for the pregnant woman with GDM, warning signs to stop exercise and seek medical attention are summarised in Table 23.3.

Conclusion

There are many benefits to be gained from participating in regular exercise during pregnancy. Furthermore, there is a growing body of evidence to suggest benefits of regular exercise for a women diagnosed with GDM and her offspring. Yet, many women are not sufficiently active to achieve these benefits, highlighting the need for further research to increase maternal exercise participation, as well as to determine the optimal frequency, intensity, duration and mode of exercise prescription for women with GDM. Specifically, approaches to overcome barriers to exercise, optimise compliance to an exercise programme, and integrate exercise into clinical practice in obstetric hospitals are essential. In fact, pregnancy may be one of the most important times to adopt a routine of regular exercise given that lifestyle during pregnancy imprints the future health of the child [43]. Furthermore, diagnosis of GDM may provide a unique opportunity for the implementation of exercise interventions given the frequent patient interaction with maternity care services, together with the potential for enhanced motivation for the benefit of a woman's unborn child.

References

1. Kramer MS, McDonald SW. Aerobic exercise for women during pregnancy. Cochrane Database of Syst Rev 2006;3. Art. No.:CD000180.
2. Sui Z, Grivell RM, Dodd JM. Antenatal exercise to improve outcomes in overweight or obese women: a systematic review. Acta Obstet Gynecol Scand. 2012;91(5):538–45.
3. Barakat R, Pelaez M, Montejo R, Luaces M, Zakynthinaki M. Exercise during pregnancy improves maternal health perception: a randomized controlled trial. Am J Obstet Gynecol. 2011;204(5):402.e1–7.
4. Daley AJ, Foster L, Long G, Palmer C, Robinson O, Walmsley H, Ward R. The effectiveness of exercise for the prevention and treatment of antenatal depression: systematic review with meta-analysis. BJOG. 2015;122:57–63.
5. Lynch AM, McDonald S, Magann EF, Evans SF, Choy PL, Dawson B, Blanksby BA, Newnham JP. Effectiveness and safety of a structured swimming program in previously sedentary women during pregnancy. J Matern Fetal Neonatal Med. 2003;14(3):163–9.

6. Clapp JF 3rd. The course of labor after endurance exercise during pregnancy. Am J Obstet Gynecol. 1990; 163(6 Pt 1):1799–805.
7. Kardel KR, Johansen B, Voldner N, Iversen PO, Henriksen T. Association between aerobic fitness in late pregnancy and duration of labor in nulliparous women. Acta Obstet Gynecol Scand. 2009;88(8):948–52.
8. Blaize AN, Pearson KJ, Newcomer SC. Impact of maternal exercise during pregnancy on offspring chronic disease susceptibility. Exerc Sport Sci Rev. 2015;43(4):198–203.
9. May LE, Scholtz SA, Suminski R, Gustafson KM. Aerobic exercise during pregnancy influences infant heart rate variability at one month of age. Early Hum Dev. 2014;90(1):33–8.
10. Avery MD, Walker AJ. Acute effect of exercise on blood glucose and insulin levels in women with gestational diabetes. J Matern Fetal Med. 2001;10(1):52–8.
11. Davenport MH, Mottola MF, McManus R, Gratton R. A walking intervention improves capillary glucose control in women with gestational diabetes mellitus: a pilot study. Appl Physiol Nutr Metab. 2008;33(3):511–7.
12. Halse RE, Wallman KE, Newnham JP, Guelfi KJ. Home-based exercise training improves capillary glucose profile in women with gestational diabetes. Med Sci Sports Exerc. 2014;46(9):1702–9.
13. García-Patterson A, Martín E, Ubeda J, María MA, de Leiva A, Corcoy R. Evaluation of light exercise in the treatment of gestational diabetes. Diabetes Care. 2001;24(11):2006–7.
14. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med. 1998;49(1):235–61.
15. Lesser KB, Gruppuso PA, Terry RB, Carpenter MW. Exercise fails to improve postprandial glycemic excursion in women with gestational diabetes. J Matern Fetal Med. 1996;5(4):211–7.
16. Jovanovic-Peterson L, Durak EP, Peterson CM. Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes. Am J Obstet Gynecol. 1989;161(2):415–9.
17. de Barros MC, Lopes MA, Francisco RP, Sapienza AD, Zugaib M. Resistance exercise and glycemic control in women with gestational diabetes mellitus. Am J Obstet Gynecol. 2010;203(6):556.e1–6.
18. Avery MD, Leon AS, Kopher RA. Effects of a partially home-based exercise program for women with gestational diabetes. Obstet Gynecol. 1997;89(1):10–5.
19. Brankston GN, Mitchell BF, Ryan EA, Okun NB. Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus. Am J Obstet Gynecol. 2004;190(1):188–93.
20. Halse RE, Wallman KE, Dimmock JA, Newnham JP, Guelfi KJ. Home-based exercise improves fitness and exercise attitude and intention in women with GDM. Med Sci Sports Exerc. 2015;47(8):1698–704.
21. Clapp JF 3rd. Long-term outcome after exercising throughout pregnancy: fitness and cardiovascular risk. Am J Obstet Gynecol 2008;199(5):489.e1–6.
22. Barakat R, Pelaez M, Lopez C, Lucia A, Ruiz JR. Exercise during pregnancy and gestational diabetes-related adverse effects: a randomised controlled trial. Br J Sports Med. 2013;47(10):630–6.
23. Dempsey JC, Sorensen TK, Williams MA, et al. Prospective study of gestational diabetes mellitus risk in relation to maternal recreational physical activity before and during pregnancy. Am J Epidemiol. 2004;159(7):663–70.
24. Ong MJ, Guelfi KJ, Hunter T, Wallman KE, Fournier PA, Newnham JP. Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. Diabetes Metab. 2009;35(5):418–21.
25. Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24–28 weeks: a randomised controlled trial. Br J Sports Med. 2012;46(9):656–61.
26. Stafne SN, Salvesen KÅ, Romundstad PR, Eggebø TM, Carlsen SM, Mørkved S. Regular exercise during pregnancy to prevent gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2012;119(1):29–36.
27. Nobles C, Marcus BH, Stanek EJ 3rd, et al. Effect of an exercise intervention on gestational diabetes mellitus: a randomized controlled trial. Obstet Gynecol. 2015;125(5):1195–204.
28. Cordero Y, Mottola MF, Vargas J, Blanco M, Barakat R. Exercise is associated with a reduction in gestational diabetes mellitus. Med Sci Sports Exerc. 2015;47(7):1328–33.
29. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. Int J Obes. 2015;39(4):642–9.
30. Guelfi KJ, Ong MJ, Crisp NA, Fournier PA, Wallman KE, Grove JR, Doherty DA, Newnham JP. Regular exercise to prevent the recurrence of gestational diabetes mellitus: a randomized controlled trial. Obstet Gynecol. 2016; 128(4):819–27.
31. Evenson KR, Barakat R, Brown WJ, Dargent-Molina P, Haruna M, Mikkelsen EM, Mottola MF, Owe KM, Rousham EK, Yeo S. Guidelines for physical activity during pregnancy: comparisons from around the world. Am J Lifestyle Med. 2014;8(2):102–21.
32. Brown WJ, Bauman AE, Bull FC, Burton NW. Development of evidence-based physical activity recommendations for adults (18–64 years). Report prepared for the Australian Government Department of Health, August 2012.
33. Metzger BE1, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 2007;30 Suppl 2:S251–60.
34. Wolfe LA, Mottola MF. PARmed-X for pregnancy. Ottawa, Ont: Can Soc Exerc Physiol; 2015.

35. Davenport MH, Charlesworth S, Vanderspank D, Sopper MM, Mottola MF. Development and validation of exercise target heart rate zones for overweight and obese pregnant women. Appl Physiol Nutr Metab. 2008;33:984–9.
36. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.
37. Ruchat SM, Davenport MH, Giroux I, Hillier M, Batada A, Sopper MM, McManus R, Hammond JA, Mottola MF. Effect of exercise intensity and duration on capillary glucose responses in pregnant women at low and high risk for gestational diabetes. Diabetes Metab Res Rev. 2012;28(8):669–78.
38. Katz VL. Water exercise in pregnancy. Semin Perinatol. 1996;20(4):285–91.
39. Halse RE, Wallman KE, Newnham JP, Guelfi KJ. Pregnant women exercise at a higher intensity during 30 min of self-paced cycling compared with walking during late gestation: implications for 2 h postprandial glucose levels. Metabolism. 2013;62(6):801–7.
40. Connelly M, Brown H, van der Pligt P, Teychenne M. Modifiable barriers to leisure-time physical activity during pregnancy: a qualitative study investigating first time mother's views and experiences. BMC Pregnancy Childbirth. 2015;15:100.
41. Guelfi KJ, Wang C, Dimmock JA, Jackson B, Newnham JP, Yang H. A comparison of beliefs about exercise during pregnancy between Chinese and Australian pregnant women. BMC Pregnancy Childbirth. 2015;15:345.
42. Symons Downs D, Ulbrecht JS. Understanding exercise beliefs and behaviors in women with gestational diabetes mellitus. Diabetes Care. 2006;29(2):236–40.
43. Gluckman PD, Hanson MA, Cooper C, Thornburg LKL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61–73.

Part VII
Postpartum Effects of Gestational Diabetes

Chapter 24
Postpartum Glucose Intolerance in Gestational Diabetes

Antonio Brunetti, Ida Pastore, Rossella Liguori and Eusebio Chiefari

Key Points

- Prevalence of gestational diabetes mellitus (GDM) is increasing worldwide with corresponding trends in obesity, type 2 diabetes (T2D) mellitus, and advancing maternal age.
- Women with GDM have increased risk of developing glucose intolerance after pregnancy.
- Both antepartum and postpartum factors may predict postpartum glucose intolerance.
- Early postpartum oral glucose tolerance test (OGTT) in women with previous GDM is needed to exclude persistency of glucose intolerance.
- The early treatment of pregnant women with prediabetes can prevent future onset T2D and its related complications.
- The rate of postpartum screening for abnormal glucose tolerance in women who had GDM still remains disappointingly low in many countries.

Keywords Gestational diabetes mellitus · Glucose intolerance · Prediabetes · Impaired glucose tolerance · Impaired fasting glucose · Postpartum screening · Oral glucose tolerance test · Antepartum predictors · Postpartum predictors

Abbreviations

ACOG	American Congress of Obstetricians and Gynecologists
ADA	American Diabetes Association
ADIPS	Australasian Diabetes in Pregnancy Society
BMI	Body Mass Index
CDA	Canadian Diabetes Association
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HbA1c	Hemoglobin A1c

A. Brunetti (✉) · I. Pastore · R. Liguori · E. Chiefari
Department of Health Sciences, University "Magna Græcia" of Catanzaro, Viale Europa (Loc. Germaneto), Catanzaro, Italy
e-mail: brunetti@unicz.it; brunetti.a@gmail.com

I. Pastore
e-mail: idapastore85@gmail.com

R. Liguori
e-mail: rossellaliguori84@gmail.com

E. Chiefari
e-mail: echiefari@libero.it

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_24

IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
NICE	National Institute of health and Care Excellence
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
T2D	Type 2 Diabetes

Introduction

According to the American Diabetes Association's (ADA) most recent criteria [1], GDM is defined as the type of glucose intolerance that typically develops in the second and third trimester of pregnancy, leading to hyperglycemia of variable extent. It has recently acquired great relevance for the public healthcare system, given the growing incidence (up to 20% of pregnancies) [1] and its association with severe short-term complications, such as gestational hypertension, fetal macrosomia, shoulder dystocia, and cesarean delivery [2]. On the other hand, GDM increases the risk for a number of longer term adverse outcomes, including progression to T2D and cardiovascular disease [3]. In this regard, although most of GDM women do not develop T2D later in life, a history of GDM confers an increased risk for T2D with respect to the predicted risk in nonpregnant women [4]. Based on these considerations, tighter diagnostic criteria for GDM have been recently introduced by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), together with specific recommendations for early postpartum screening of women with a history of GDM aimed at preventing prediabetes [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] or overt T2D [1]. In this chapter, we focus on the prevalence of glucose intolerance in postpartum, its pathogenetic mechanism(s), the antepartum and postpartum predictor factors, the guidelines for the diagnosis, and current recommendations for its prevention and treatment.

Epidemiology

T2D is the most common metabolic disease, with a rapidly increasing incidence and prevalence worldwide [5]. The latest estimate from the International Diabetes Federation http://www.idf.org (accessed April 30, 2016) indicates a global prevalence rate of more than 8% in adults, while it is predicted that by 2030 diabetes will afflict over 500 million people in the world [5]. In parallel, the incidence of T2D has increased dramatically in women of reproductive age, as well as the incidence of GDM [6], which represents a risk factor for future T2D [3]. Today, despite of the wide variations due to ethnic differences and different diagnostic criteria used, the incidence of GDM exceeds 25% of screened pregnancies [7]. On the other hand, recent lines of evidence indicate that any degree of abnormal glucose homeostasis during gestation, even if not meeting criteria for GDM, is predictive for increased risk of postpartum prediabetes and overt T2D [8].

A list of studies showing the rate of prediabetes (IFG/IGT) and overt T2D in postpartum women with previous GDM is provided in Table 24.1, using the current ADA cut-offs for diagnosis [1]. Differences in the ethnic groups examined (higher rate in Latin, South Asian, and Turkish), as well as

Table 24.1 Prevalence of postpartum glucose intolerance (IFG/IGT or T2D) in different ethnic groups, as measured by FPG and/or OGTT, using current ADA criteria

Study	Country	Ethnicity	Women with GDM (n)	Screened women (%)	IFG/IGT (%)	T2D (%)
Buchanan et al. [9]	USA	Latin	122	100	50.0	10.0
Schaefer-Graf et al. [10]	USA	Multiethnic	1636	100	26.0	14.1
Jang et al. [11]	South Korea	Asian	392	79.3	23.2	15.1
Russell et al. [12]	USA	Multiethnic	344	45	28.0	8.0
Kitzmiller et al. [13]	USA	Multiethnic	527	100	29.6	4.7
Hunt et al. [14]	USA	Mexican, Mexican American	707	57	36.1	4.5
Feig et al. [15]	Canada	Multiethnic	21,823	100	–	3.7
Ogonowski and Miazgowski [16]	Poland	Caucasian	855	37.2	12.2	1.3
Ferrara et al. [17]	USA	Multiethnic	14,448	38.2	31.3	2.7
Kwong et al. [18]	Canada	Multiethnic	909	48.2	17.0	3.2
Lawrence et al. [19]	USA	Multiethnic	11,825	50.2	16.3	1.1
Kerimoglu et al. [20]	Turkey	Caucasian	109	71.6	35.9	34.6
Stasenko et al. [21]	USA	Multiethnic	745	33.7	28.3	2.0
Kim et al. [22]	South Korea	Asian	381	100	44.8	5.2
Katon et al. [23]	USA	Multiethnic	277	100	37.2	5.4
Kwak et al. [24]	South Korea	Asian	843	100	–	12.5
Mendez-Figueroa et al. [25]	USA	Multiethnic	414	48.6	34.3	3.0
Capula et al. [26]	Italy	Caucasian	1342	33.8	32.1	4.0
Benhalima et al. [27]	Belgium	Caucasian	231	78.6	39.1	5.3
Weinert et al. [28]	Brazil	Latin	209	51.7	20.4	3.7
Cho et al. [29]	South Korea	Asian	1686	44.9	44.1	18.4

variations in the criteria employed for the diagnosis of GDM and postpartum glucose intolerance may explain the different rates observed among these studies, together with the possibility that in some of these investigations women with preexisting T2D might have been included considering that universal screening for undiagnosed diabetes in early pregnancy was unusual in the past. Moreover, it must be considered the increasing rates of postpartum glucose intolerance over the last decades, due to the recent trends in obesity and advancing maternal age [6].

In a large meta-analysis of 20 cohort studies, it has been shown that women with GDM had over sevenfold increased risk of developing T2D compared to women with normoglycemic pregnancy. As reported in this meta-analysis, the risk was influenced by ethnicity, duration of follow-up and diagnostic criteria [30]. In another study, analyzing over 600,000 deliveries in Canada, the rates of T2D among women with previous GDM increased rapidly during the first months postpartum and continued to increase in the following years, so that the probability of developing diabetes, after delivery, was 3.7% at 9 months and 18.9% at 9 years among women with previous GDM, compared to 0.0–2.0%, respectively, among women without GDM [31].

Etiology

T2D is a common, heterogeneous disease in which a complex interplay of genetic and environmental factors may influence disease onset and progression [32]. Although not completely understood, the role of genetics in T2D is well documented [32], whereas a more westernized lifestyle, which is responsible for excess weight and obesity in modern adult's life is the best characterized environmental factor known to affect T2D risk [32] through its impact on insulin resistance, which represents the initial step in the development of T2D. Initially, in individuals in whom T2D is destined to develop, the pancreatic β-cell compensates for peripheral insulin resistance by secreting more insulin [32]. Hyperglycemia in insulin-resistant individuals will develop later when β-cells fail to compensate and diabetes ensues [32] (Fig. 24.1). During pregnancy, peripheral insulin resistance is favored by the increased maternal adiposity that occurs during the perinatal period, and by the release of adipocytokines and placenta-derived hormones (i.e., prolactin, chorionic somatomammotropin, steroid hormones) which act by decreasing insulin sensitivity, thereby facilitating the development of glucose intolerance and GDM [33]. The adverse effects on glucose homeostasis, during pregnancy, are usually attenuated after delivery and removal of the placenta, with return to normal glucose status within 6–12 weeks postpartum.

Factors that may influence the risk of postpartum glucose intolerance include the use of progestin-only contraception, additional pregnancies and the degree of abnormal glucose homeostasis during and soon after pregnancy [34, 35]. Also, recent evidences suggest that alterations in leptin signaling and fetuin-A, a hepatic secretory protein that has recently been implicated in insulin resistance, may contribute to the pathogenesis of T2D in women with recent GDM [36]. The mediating role of insulin resistance in these conditions is supported by the observation that weight loss and medications to improve peripheral insulin sensitivity, like metformin, can slow down or even prevent T2D in women with previous GDM [37]. On the other hand, hyperinsulinemia, a marker of insulin resistance, by adversely affecting vascular reactivity and atherogenesis, may explain the increased risk for cardiovascular disease in women with previous GDM who exhibit characteristics similar to those of patients with the metabolic syndrome, the umbrella term for a cluster of risk factors which include insulin resistance, glucose intolerance, central obesity, hypertriglyceridemia, and low HDL-cholesterol [38].

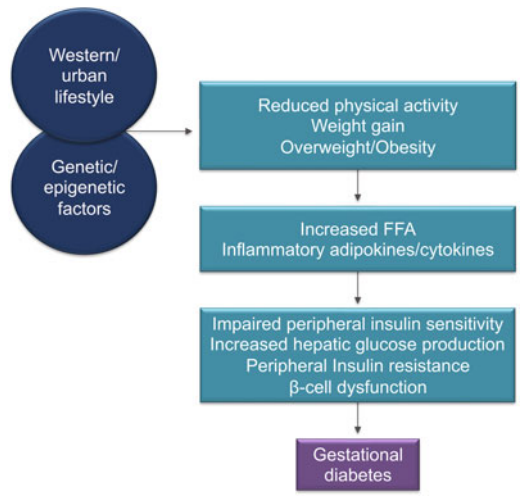


Fig. 24.1 Pathogenesis of GDM. As pregnancy progresses, both hepatic and peripheral insulin resistance occur as pregnant women gain weight and reduce physical activity. Glucose intolerance develops and pancreatic *β*-cell function deteriorates, leading to GDM. FFA (Free Fatty Acids)

Based on the above considerations, it appears clear that when insulin secretion does not increase sufficiently to counteract the insulin-resistant state during pregnancy, hyperglycemia becomes overt, thereby leading to a diagnosis of GDM, which develops as a consequence of pancreatic β-cell dysfunction in pregnant women (Fig. 24.1). The defect in β-cell function is not specific to pregnancy, as, in most cases, it exists before and after pregnancy [39], and it is very often progressive [40], thus conferring a high risk of developing overt T2D for many years after pregnancy [39]. These findings have been supported recently by genetic studies showing the association of gene variants and GDM susceptibility. Most of these genetic variants are also found in common T2D, and have been associated with defects in β-cell function and insulin secretion [41].

Predictors of Postpartum Glucose Intolerance

So far, many antepartum and postpartum clinical and biochemical predictors of postpartum glucose intolerance have been identified in women with GDM (Table 24.2). Although no consistent results exist in this scenario (Table 24.3), knowledge of these predictors is important for postpartum surveillance of women with GDM, given that some of them can be attenuated (or even reversed) by improving lifestyle behaviors, particularly exercise and diet. Among the unmodifiable antepartum risk factors, genetic variants in three genes, *CDKN2A/2B*, *HHEX*, and *CDKAL1*, have been identified as reliably linked to postpartum T2D [24], whereas genetic prediction of postpartum T2D has been proposed in women with GDM carrying polymorphisms in the *TCF7L2* and *FTO* genes [51], two genes whose association to common T2D has been established [32], thus further supporting the tight correlation between GDM and T2D. Other unmodifiable factors include ethnicity (i.e. South Asian) [52], family history of diabetes [26, 49], an older age at pregnancy, parity, early GDM, and GDM in previous pregnancies [26]. However, no association of postpartum T2D risk with gestational age, age at diagnosis of GDM, and the number of earlier and subsequent pregnancies was found in a UK-based cohort of women with GDM [53], indicating that further studies are needed to refine these relationships.

Observations from a systematic review of prospective studies of antepartum glucose tolerance test results indicate that FPG, OGTT 2 h-blood glucose, and OGTT glucose AUC (area under the curve) are strong and consistent predictors of postpartum glucose intolerance and T2D among women with GDM [54]. Antepartum and postpartum hemoglobin A1c (HbA1c) has also been evaluated as a potential predictor of postpartum glucose intolerance with non-univocal results. Whereas an association was established between HbA1c measured at GDM diagnosis and postpartum abnormal glucose tolerance [23, 49, 50], no association was reported in other investigations [55]. It is suggested that the utility of HbA1c early after delivery is inferior to the OGTT for the detection of early disturbances in glucose metabolism; however, increased levels of HbA1c could serve as an indicator of risk for postpartum T2D [55]. Reduced β-cell function and decreased insulin sensitivity were

Table 24.2 Antepartum and postpartum predictors of glucose intolerance

Antepartum predictors	Postpartum predictors
• Advanced maternal age at pregnancy • Family history of T2D • High pre-pregnancy BMI • Previous GDM • Earlier diagnosis of GDM • Insulin therapy during pregnancy • High FPG on antepartum OGTT • PCOS	• High postpartum BMI • High postpartum HbA1c • High glucose at 2 h postpartum OGTT • β-cell dysfunction • No breastfeeding • High serum triacylglycerols • High energy and fat intake

Table 24.3 Predictors of postpartum glucose intolerance as reported in different studies

Study	Screened women (n)	Predictors
Catalano et al. [42]	103	High FPG at the time of OGTT during pregnancy, earlier gestational age at GDM diagnosis, abnormal pregravid BMI and delivery weight, need for insulin therapy during pregnancy, macrosomia
Buchanan et al. [43]	122	Pancreatic β-cell dysfunction, earlier diagnosis of GDM, weight gain
Pallardo et al. [44]	637	Pre-pregnancy obesity and severity of GDM, low C-peptide/glucose score during pregnancy, earlier gestational age at GDM diagnosis, previous GDM
Aberg et al. [45]	229	Maternal age >40 years, a high 2 h glucose value at OGTT during pregnancy, insulin need during pregnancy
Sharefer et al. [10]	1636	High FPG and OGTT AUC during pregnancy, earlier diagnosis of GDM and previous GDM
Albareda et al. [46]	696	Antepartum hyperglycemia, four abnormal glucose levels at OGTT or overt T2D during pregnancy, gestational age at diagnosis of GDM <24 weeks, pre-pregnancy BMI ≥ 26.4 kg/m^2
Jang et al. [11]	311	High pre-pregnancy weight, earlier diagnosis of GDM, high 2 h glucose and 1 or 3 h insulin values during diagnostic OGTT
Lee et al. [47]	783	Insulin need, Asian ethnicity, high 1 h glucose value at OGTT during pregnancy
Retnakaran et al. [48]	137	High antepartum OGTT AUC, index of insulin resistance
Ekelund et al. [49]	174	Abnormal values of HbA1c and FPG during pregnancy, family history of T2D, previous pregnancies
Kim et al. [22]	381	High BMI during antepartum and postpartum, pancreatic β-cell dysfunction, family history of T2D, high serum triacylglycerols, elevated energy and fat intake during postpartum, high postpartum HbA1c
Katon et al. [23]	277	Increased HbA1c at diagnosis of GDM
Kwak et al. [24]	843	High pre-pregnancy BMI, high antepartum OGTT AUC, pancreatic β-cell dysfunction, *CDKN2A/2B* and *HHEX* gene variants
Capula et al. [26]	454	Advanced age at pregnancy, family history of T2D, high pre-pregnancy BMI, previous GDM, insulin therapy during pregnancy, high FPG, previous PCOS
Weinert et al. [28]	108	Family history of T2D, insulin need during pregnancy, cesarean section
Liu et al. [50]	1263	Pre-pregnancy obesity and weight gain from pre-pregnancy to postpartum, high 2 h glucose value at OGTT, and HbA1c during pregnancy

reported to be strong predictors of postpartum glucose intolerance in several studies [11, 22, 43, 44]. Consistently, women with GDM who needed insulin therapy during pregnancy had an increased risk of developing prediabetes or overt T2D during postpartum [28, 45, 48]. An association with postpartum glucose intolerance has been reported in women with pre-pregnancy diagnosis of polycystic ovary syndrome (PCOS) [26], increased pre-pregnancy BMI and high gestational weight gain [11, 24, 26, 50], as well as in women with additional pregnancies [26, 49], all conditions that are known to be often associated with insulin resistance an T2D. By examining additional, potentially modifiable predictors, such as maternal diet during pregnancy, physical activity, and breastfeeding, it was found that the amount of animal fat intake was higher among women with postpartum prediabetes and T2D as compared to women with normal glucose tolerance, whereas breastfeeding had no influence on the risk of developing postpartum diabetes [22]. However, with respect to this latter point, the hypothesis that breastfeeding associates with a reduction in the risk of postpartum T2D is supported by other findings [56].

Diagnosis of Postpartum Glucose Intolerance

Early diagnosis of GDM is crucial to improve outcomes and addressing the subject to selective screening in order to prevent the development of T2D and its complications, including cardiovascular disease [38]. Concerning this point, a wide consensus exists on the importance of the postpartum period for early identification and management of issues useful for planning prevention and intervention strategies [38]. This consensus is based on the studies that lend support to this conclusion, indicating that: (1) the prevalence of prediabetes or overt T2D is high in the postpartum period [11]; (2) postpartum glucose abnormalities may help identifying women at increased risk to develop T2D later in life [30]; (3) lifestyle intervention (diet, physical activity, weight management) and drug therapy [metformin, insulin sensitizer thiazolidinediones (TZDs)] can effectively delay or even prevent T2D in women with postpartum glucose intolerance [37]; (4) the risk for cardiovascular disease is higher among women with prior GDM [38]; (5) congenital malformations are increased in infants of women with postpartum hyperglycemia entering subsequent pregnancy [38]. Consistent with these assumptions, the Fifth International Workshop-Conference on Gestational Diabetes Mellitus Panel recommends that GDM women have a 2 h 75 gr OGTT at 6 weeks to 12 weeks postpartum [38]. However, as no common agreement exists on this point, defining the best screening strategy for glucose intolerance in early postpartum among women with a history of GDM is still debated, and different screening tests are available each with its own pros and cons (Table 24.4). Although the majority of studies indicate the 2 h 75 gr OGTT as the most sensitive tool for postpartum glucose screening for women previously diagnosed with GDM [38], it must be pointed out that the rate of postpartum screening remains disappointingly low and the majority of women fail to return for postpartum OGTT, thereby supporting the need for alternative testing methods [57]. In this regard, FPG has been evaluated in postpartum screening of glucose intolerance. Although FPG had greater reproducibility compared with OGTT, it lacked sensitivity in identifying women with IGT or T2D and has been considered inadequate to detect postpartum hyperglycemia [38, 58]. The utility of HbA1c in the early postpartum screening of women with GDM has also been investigated [59]. However, poor concordance has been found between the HbA1c and OGTT for the diagnosis of prediabetes and T2D following GDM, with HbA1c less efficacious in identifying cases of diabetes in women in the post-GDM period. Moreover, the accuracy of HbA1c measurements can be adversely affected by factors that alter the HbA1c value, including variability in erythrocyte life span, conditions that decrease erythropoiesis, chronic kidney disease, severe hypertriglyceridemia, chronic alcoholism, and interindividual variation in HbA1c [60].

Table 24.4 Postpartum glucose screening tests: pros and cons

Test	Pros	Cons
FPG	• Fast • Low cost • High reproducibility • Widely available	• Sensitivity less than OGTT • Single-point blood glucose value • Low sample stability
2 h OGTT	• High sensitivity • High specificity • Early marker of IGT	• Time-consuming • Expensive • Low reproducibility • Low sample stability
HbA1c	• Fast • No fasting required • Sample stability	• Expensive • Low sensitivity • Not available in certain regions of the world • HbA1c interference http://www.ngsp.org/interf.asp (accessed April 30, 2016)

Rate of Postpartum Screening and Strategies for Its Improvement

Emerging evidence suggests that women that do not attend a postpartum screening following GDM have an increased risk to develop T2D later in their lives [49]. However, although, postpartum screening is critical for early identification of glucose intolerance in women who develop diabetes while pregnant, its rate remains still relatively low, ranging from 23 to 54%, depending on the population [12, 61, 62]. As reported before, common barriers to postpartum screening may include lack of patient understanding and awareness, lack of interest in patient's personal health, some concern over the current recommendations, poor communication between antepartum and postpartum staff, lack of family support, socioeconomic, and racial/ethnic factors [12, 18, 61]. Based on this background, early intervention strategies and tools have been proposed and developed in the last years to help improving adherence to postpartum screening. They include education intervention among women with prior GDM, automated orders to healthcare providers, mobile phone-based short messaging service and email reminder messages to patients, antepartum written and verbal counselling, continuous postpartum follow-up, and more [38, 61, 63]. For example, women who were older or experienced greater contact with medical care had greater postpartum screening than young mothers who may erroneously believe they are too young to develop diabetes [12, 21, 58, 61, 62]. Also, women who were more likely to be screened had higher educational attainment and higher income [19, 61, 62], whereas women with obesity and higher parity attended screening less frequently [18, 19, 62]. Greater postpartum screening was observed in women with earlier diagnosis of GDM [61, 62], as well as in women with previous GDM [61], who might have had some basic knowledge of the disease and its likely progression and potential complications [64]. In this regard, patients with a previous diagnosis of PCOS were found to be significantly associated with a higher compliance rate for postpartum testing [61]. Time flexibility and active involvement from healthcare providers are among the interventions that seem to facilitate the return rate for postpartum screening test for women with a known history of GDM. In this respect, as has been pointed out, the perfect time to remind women to stay on schedule with postpartum screening would be at the time they came to the hospital for baby's immunizations [64].

Guideline Recommendations

Postpartum Screening: How and When?

The rationale for postpartum glucose testing is to detect any type of glucose intolerance (IFG, IGT, or overt diabetes) after pregnancy in women who developed diabetes while pregnant [65]. As outlined in Table 24.5, current guidelines from the ADA, the Fifth International Workshop-Conference on Gestational Diabetes Mellitus, the ADIPS, and the Endocrine Society recommend that all women who develop diabetes while pregnant undergo a postpartum OGTT 6–12 weeks after their delivery date. The same test is also advocated by the Canadian Diabetes Association (CDA), which, however, recommends a longer period of follow-up (6 weeks to 6 months postpartum), while the American Congress of Obstetricians and Gynecologists (ACOG) recommends all women with GDM be screened at 6–12 weeks postpartum with either a FPG test or a 75 gr 2 h OGTT (Table 24.5). If these test results remain normal, women will still need to be screened every 1–3 years depending on the presence of other risk factors (such as family history of diabetes, high pre-pregnancy BMI, need for glucose-lowering agents during pregnancy) [1]. Also, the current ADIPS guidelines recommend annual OGTT screening in women contemplating further pregnancy, whereas for women at lower risk, a FPG every 1–2 years is considered to be sufficient. Despite this, in 2015, NICE recommended

Table 24.5 Postpartum screening recommendations for women with GDM

Proposer	Time	Test
ADA [1] Fifth International Workshop-Conference on GDM [38] ADIPS http://www.adips.org (accessed April 30, 2016) Endocrine Society http://www.endocrine.org (accessed April 30, 2016)	6–12 week postpartum	2 h 75 gr OGTT
NICE http://www.nice.org.uk/guidance/ng3 (accessed April 30, 2016)	6–13 week postpartum	FPG
CAD http://www.diabetes.ca (accessed April 30, 2016)	6 week–6 months postpartum	2 h 75 gr OGTT
ACOG http://www.acog.org (accessed April 30, 2016)	6–12 weeks postpartum	2 h 75 gr OGTT or FPG

either a FPG or HbA1c test rather than OGTT for postpartum screening (Table 24.5). NICE also suggests an annual HbA1c test to women who are diagnosed with GDM who have a negative postpartum diabetes screening test http://www.nice.org.uk/guidance/ng3 (accessed April 30, 2016).

Management of Postpartum Glucose Intolerance

GDM usually goes away after delivery, and most women will have normal glucose values in the immediate postpartum period. However, if glucose intolerance (IFG/IGT) is confirmed by fasting laboratory values or casual glucose tests [1], lifestyle interventions promoting a healthful diet, physical activity, and weight loss are mandatory to prevent diabetes risk and improve the lifelong health of these women. First, healthful dietary patterns including eating vegetables, fruit, seafood, white meat, and avoiding sugar-sweetened beverage, and red and processed meats may lower T2D risk among women with a GDM history [66]. Second, 30–60 min daily aerobic physical activity (at least 5 days per week) is an effective tool for improving peripheral insulin sensitivity and blood glucose levels, and exerts positive effects on cardiovascular function, mood, and on psychological wellbeing [1]. Third, breastfeeding immediately after delivery and during the first year has been associated with both short- and long-term benefits for the infant (i.e., reduced neonatal hypoglycemia and reduced risk of developing overweight and obesity during childhood), and reduced risk for subsequent obesity and T2D in many breastfeeding women http://guidelines.diabetes.ca/fullguidelines/Chapter36#bib291 (accessed April 30, 2016). The addition of pharmacotherapy is supported in women with persisting IGT when lifestyle interventions alone fail to obtain the desired improvements [13]. In this regard, metformin, by decreasing glucose production and fat mass in visceral adipose tissue, ameliorates peripheral insulin sensitivity and contributes to weight loss, thereby preventing or delaying the progression from IGT to T2D among high-risk women [37]. Metformin in breast milk is generally low, and no harmful effects have been reported in children of mothers taking metformin [13]. In diet-treated patients, acarbose may help controlling postprandial blood glucose levels by delaying carbohydrate absorption. However, side effects limit its usage, whereas there are no studies on the effect of acarbose on lactation quality [13]. As PPAR-γ agonists, TZDs act by increasing insulin sensitivity, thus contributing to protecting overworked pancreatic β-cells from failure. As for acarbose, experience is limited on the use of TZDs (pioglitazone or rosiglitazone) in diabetic lactating women. Women with prior GDM who develop overt T2D in the early postpartum period deserve the same therapeutic approach as the general diabetic population, and, if necessary, any type of insulin can be used during breastfeeding or bottlefeeding to ensure whole-body glucose homeostasis.

Future Pregnancy and Contraception

Virtually all medical societies strongly recommend that women who develop diabetes while pregnant should be counseled about future pregnancies [38]. Glucose intolerance should be identified and corrected in order to assure normoglycemia at the moment of conception. These steps are crucial to reduce maternal morbidity and the risk of congenital malformations, and to minimize the possibility of current or future unfavorable obstetric outcomes [13], and the children's risk of adult-onset chronic diseases, including cardiovascular and metabolic diseases [67]. Also, it must be considered that a new pregnancy in a women who has had GDM before, provides a clearly increased risk of lifelong T2D [35]. Care by an interdisciplinary healthcare team that includes diabetologists and obstetricians, diabetes nurse educators and dietitians, prior to conception and during pregnancy, was found to be effective in minimizing maternal and neonatal outcomes in women with preexisting diabetes [68]. Nevertheless, adherence to preconception healthcare programs attempting to improve general health and life style remains limited and largely unheeded among women with prior GDM and postpartum glucose intolerance [13]. Preconception/interconception healthcare programs for high-risk women may include contraception. All women with prediabetes or T2D should be made aware of the importance of taking preventive measures encouraging the use of contraceptive methods in preparation for subsequent pregnancies. All the contraceptive options available can be considered by most patients. However, low-dose combination oral contraceptives should be preferred, starting 6–8 weeks after delivery if woman is breastfeeding. Instead, progestin-only oral contraceptives should be used with caution during breastfeeding, due to the potential for increased T2D risk [18].

In Summary

- Counseling is an effective tool in increasing antepartum and postpartum screening in women with GDM who are at elevated risk for future T2D.
- Women who were diagnosed with GDM should undergo test blood glucose to exclude persisting hyperglycemia before they are transferred to community care.
- An individualized surveillance strategy is recommended to optimize postpartum follow-up for GDM women with the purpose of improving adherence rate.
- Women with GDM are encouraged to breastfeed immediately after birth and for at least 3 months afterwards.
- Lifestyle recommendations, including weight control, diet, and exercise should be considered for all women with GDM.
- Women with GDM should undergo OGTT (or FPG) determination at 6–12 weeks postpartum.
- For women with GDM and postpartum glucose intolerance a pre-pregnancy consultation is recommended before the next pregnancy.
- Women with postpartum glucose intolerance should be advised about the risk of early abortion and congenital deformities of the fetus if hyperglycemia is not corrected before the next pregnancy.
- Women with GDM and prediabetes should be advised about the possibility of preventing overt T2D and the risk of hypertension and cardiovascular disease.
- Offspring of women with GDM are at higher risk of obesity and T2D during childhood and young adult age.

Conclusions

Women who develop diabetes while pregnant are at elevated risk for T2D later in life. Early postpartum screening in these women is important to timely detect glucose abnormalities and start lifestyle modifications as early as possible to prevent future diabetes. Nevertheless, for a variety of reasons, the rate of adherence to postpartum glucose testing in women with a history of GDM is poor and long-term success is modest. Strategies that include the development of educational programs aimed at improving women's participation in postpartum screening would enhance the standards of care and quality of life for women with GDM and would likely improve outcomes.

References

1. American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care. 2016;39 Suppl 1.
2. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002.
3. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25:1862–8.
4. Ratner RE. Prevention of type 2 diabetes in women with previous gestation diabetes. Diabetes Care. 2007;30(Suppl 2):S242–5.
5. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:4–14.
6. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am. 2007;34:173–99.
7. Capula C, Chiefari E, Vero A, et al. Gestational diabetes mellitus: screening and outcomes in southern italian pregnant women. ISRN Endocrinol. 2013;2013:387495.
8. Carr DB, Newton KM, Utzschneider KM, et al. Modestly elevated glucose levels during pregnancy are associated with a higher risk of future diabetes among women without gestational diabetes mellitus. Diabetes Care. 2008;31:1037–9.
9. Buchanan TA, Xiang A, Kjos SL, et al. Gestational diabetes: antepartum characteristics that predict postpartum glucose intolerance and type 2 diabetes in Latino women. Diabetes. 1998;47:1302–10.
10. Schaefer-Graf UM, Buchanan TA, Xiang A, et al. Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. Am J Obstet Gynecol. 2002;186:751–6.
11. Jang HC, Yim CH, Han KO, et al. Gestational diabetes mellitus in Korea: prevalence and prediction of glucose intolerance at early postpartum. Diabetes Res Clin Pract. 2003;61:117–24.
12. Russell MA, Phipps MG, Olson CL, et al. Rates of postpartum glucose testing after gestational diabetes mellitus. Obstet Gynecol. 2006;108:1456–62.
13. Kitzmiller JL, Dang-Kilduff L, Taslimi MM. Gestational diabetes after delivery. Short-term management and long-term risks. Diabetes Care. 2007;30(Suppl 2):S225–35.
14. Hunt KJ, Conway DL. Who returns for postpartum glucose screening following gestational diabetes mellitus? Am J Obstet Gynecol. 2008;198:404–6.
15. Feig DS, Zinman B, Wang X, et al. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ. 2008;179:229–34.
16. Ogonowski J, Miazgowski T. The prevalence of 6 weeks postpartum abnormal glucose tolerance in Caucasian women with gestational diabetes. Diabetes Res Clin Pract. 2009;84:239–44.
17. Ferrara A, Peng T, Kim C. Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: a report from the translating research into action for diabetes (TRIAD) study. Diabetes Care. 2009;32:269–74.
18. Kwong S, Mitchell RS, Senior PA, et al. Postpartum diabetes screening: adherence rate and the performance of fasting plasma glucose versus oral glucose tolerance test. Diabetes Care. 2009;32:2242–4.
19. Lawrence JM, Black MH, Hsu JW, et al. Prevalence and timing of postpartum glucose testing and sustained glucose dysregulation after gestational diabetes mellitus. Diabetes Care. 2010;33:569–76.
20. Kerimoğlu OS, Yalvaç S, Karçaaltınçaba D, et al. Incidence of diabetes mellitus at postpartum six to twelve months following the diagnosis of gestational diabetes mellitus. J Turk Ger Gynecol Assoc. 2010;11:89–94.

21. Stasenko M, Cheng YW, McLean T, et al. Postpartum follow-up for women with gestational diabetes mellitus. Am J Perinatol. 2010;27:737–42.
22. Kim SH, Kim MY, Yang JH, et al. Nutritional risk factors of early development of postpartum prediabetes and diabetes in women with gestational diabetes mellitus. Nutrition. 2011;27:782–8.
23. Katon J, Reiber G, Williams MA, et al. Hemoglobin A1c and postpartum abnormal glucose tolerance among women with gestational diabetes mellitus. Obstet Gynecol. 2012;119:566–74.
24. Kwak SH, Choi SH, Jung HS, et al. Clinical and genetic risk factors for type 2 diabetes at early or late post partum after gestational diabetes mellitus. J Clin Endocrinol Metab. 2013;98:E744–52.
25. Mendez-Figueroa H, Dahlke JD, Daley J, et al. Prediction of abnormal postpartum glucose tolerance testing in mild gestational diabetes mellitus. J Reprod Med. 2014;59:393–400.
26. Capula C, Chiefari E, Vero A, et al. Prevalence and predictors of postpartum glucose intolerance in Italian women with gestational diabetes mellitus. Diabetes Res Clin Pract. 2014;105:223–30.
27. Benhalima K, Leuridan L, Calewaert P, et al. Glucose intolerance after a recent history of gestational diabetes. Int J Endocrinol. 2014;2014:727652.
28. Weinert LS, Mastella LS, Oppermann ML, et al. Postpartum glucose tolerance status 6 to 12 weeks after gestational diabetes mellitus: a Brazilian cohort. Arq Bras Endocrinol Metabol. 2014;58(2):197–204.
29. Cho GJ, An JJ, Choi SJ, et al. Postpartum glucose testing rates following gestational diabetes mellitus and factors affecting testing non-compliance from four tertiary centers in Korea. J Korean Med Sci. 2015;30:1841–6.
30. Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373:1773–9.
31. Feig DS, Zinman B, Wang X, et al. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ. 2008;179:229–34.
32. Brunetti A, Chiefari E, Foti D. Recent advances in the molecular genetics of type 2 diabetes mellitus. World J Diabetes. 2014;5:128–40.
33. Masuzaki H, Ogawa Y, Sagawa N, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat Med. 1997;3:1029–33.
34. Xiang AH, Kawakubo M, Kjos SL, et al. Long-acting injectable progestin contraception and risk of type 2 diabetes in Latino women with prior gestational diabetes mellitus. Diabetes Care. 2006;29:613–7.
35. Peters RK, Kjos SL, Xiang A, et al. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. Lancet. 1996;347:227–30.
36. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012;148:852–71.
37. Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93:4774–9.
38. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 2007;30 (Suppl 2):S251–60.
39. Buchanan TA, Xiang A, Kjos SL, et al. What is gestational diabetes? Diabetes Care. 2007;30(Suppl 2):S105–11.
40. Kramer CK, Swaminathan B, Hanley AJ, et al. Each degree of glucose intolerance in pregnancy predicts distinct trajectories of β-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum. Diabetes Care. 2014;37:3262–9.
41. Zhang C, Bao W, Rong Y, et al. Genetic variants and the risk of gestational diabetes mellitus: a systematic review. Hum Reprod Update. 2013;19:376–90.
42. Catalano PM, Vargo KM, Bernstein IM, et al. Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. Am J Obstet Gynecol. 1991;165(4 Pt 1):914–19.
43. Buchanan TA, Xiang A, Kjos SL, et al. Gestational diabetes: antepartum characteristics that predict postpartum glucose intolerance and type 2 diabetes in Latino women. Diabetes. 1998;47:1302–10.
44. Pallardo F, Herranz L, Garcia-Ingelmo T, et al. Early postpartum metabolic assessment with prior gestational diabetes. Diabetes Care. 1999;22:1053–8.
45. Aberg AE, Jönsson EK, Eskilsson I, et al. Predictive factors of developing diabetes mellitus in women with gestational diabetes. Acta Obstet Gynecol Scand. 2002;81:11–6.
46. Albareda M, Caballero A, Badell G, et al. Diabetes and abnormal glucose tolerance in women with previous gestational diabetes. Diabetes Care. 2003;26:1199–205.
47. Lee AJ, Hiscock RJ, Wein P, et al. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes. Diabetes Care. 2007;30:878–83.
48. Retnakaran R, Qi Y, Sermer M, et al. Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. Diabetes Care. 2008;31:2026–31.
49. Ekelund M, Shaat N, Almgren P, et al. Prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetologia. 2010;53:452–7.
50. Liu H, Zhang S, Wang L, et al. Fasting and 2-hour plasma glucose, and HbA1c in pregnancy and the postpartum risk of diabetes among Chinese women with gestational diabetes. Diabetes Res Clin Pract. 2016;112:30–6.

51. Ekelund M, Shaat N, Almgren P, Groop L, Berntorp K, et al. Genetic prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetes Res Clin Pract. 2012;97:394–8.
52. Sinha B, Brydon P, Taylor RS, et al. Maternal ante-natal parameters as predictors of persistent postnatal glucose intolerance: a comparative study between Afro-Caribbeans, Asians and Caucasians. Diabetes Med. 2003;20:382–6.
53. Sivaraman SC, Vinnamala S, Jenkins D. Gestational diabetes and future risk of diabetes. J Clin Med Res. 2013;5:92–6.
54. Golden SH, Bennett WL, Baptist-Roberts K, et al. Antepartum glucose tolerance test results as predictors of type 2 diabetes mellitus in women with a history of gestational diabetes mellitus: a systematic review. Gend Med. 2009;6 (Suppl 1):109–22.
55. Göbl CS, Bozkurt L, Yarragudi R, et al. Is early postpartum HbA1c an appropriate risk predictor after pregnancy with gestational diabetes mellitus? Acta Diabetol. 2014;51:715–22.
56. O'Reilly MW, Avalos G, Dennedy MC, et al. Atlantic dip: high prevalence of abnormal glucose tolerance postpartum is reduced by breast-feeding in women with prior gestational diabetes mellitus. Eur J Endocrinol. 2011;165:953–9.
57. Venkataraman H, Sattar N, Saravanan P. Postnatal testing following gestational diabetes: time to replace the oral glucose tolerance test? Lancet Diabetes Endocrinol. 2015;3:754–6.
58. Kwong S, Mitchell RS, Senior PA, et al. Postpartum diabetes screening: adherence rate and the performance of fasting plasma glucose versus oral glucose tolerance test. Diabetes Care. 2009;32:2242–4.
59. Duke A, Yap C, Bradbury R, et al. The discordance between HbA1c and glucose tolerance testing for the postpartum exclusion of diabetes following gestational diabetes. Diabetes Res Clin Pract. 2015;108:72–7.
60. O'Keeffe DT, Maraka S, Rizza RA. HbA1c in the evaluation of diabetes Mellitus. JAMA. 2016;315:605–6.
61. Capula C, Chiefari E, Vero A, et al. Predictors of postpartum glucose tolerance testing in italian women with gestational diabetes mellitus. ISRN Endocrinol. 2013;2013:182505.
62. Ferrara A, Peng T, Kim C. Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: a report from the translating research into action for diabetes (TRIAD) study. Diabetes Care. 2009;32:269–74.
63. Halperin IJ, Sehgal P, Lowe J, et al. Increasing timely postpartum oral glucose tolerance test completion in women with gestational diabetes: a quality-improvement initiative. Can J Diabetes. 2015;39:451–6.
64. Mohd Suan MA. Return for postpartum oral glucose tolerance test following gestational diabetes mellitus. Asia Pac J Public Health. 2015;27:601–9.
65. Expert committee on the diagnosis and classification of diabetes mellitus: follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003;26:3160–7.
66. Tobias DK, Hu FB, Chavarro J, et al. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. Arch Intern Med. 2012;172:1566–72.
67. Rice GE, Illanes SE, Mitchell MD. Gestational diabetes mellitus: a positive predictor of type 2 diabetes? Intl J Endocrinol. 2012;2012:721653.
68. Wahabi HA, Alzeidan RA, Bawazeer GA, et al. Preconception care for diabetic women for improving maternal and fetal outcomes: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2010;10:63.

Chapter 25
Diet After Gestational Diabetes (GDM)

Helen M. Taylor, Lesley MacDonald-Wicks and Clare E. Collins

Key Points

- Gestational diabetes mellitus (GDM) identifies both women and their offspring as susceptible to developing metabolic syndrome and type 2 diabetes (T2DM) [1, 2].
- Intensive lifestyle interventions, in which dietary change plays a major part, can be effective for preventing or delaying T2DM [3–5], including in women with prior GDM, [5, 6] and are cost-effective, even when costed for high-intensity programs [7, 8].
- For people at risk of T2DM, weight loss and/or prevention of weight gain is key to delaying or preventing T2DM, therefore diet is a critical component of effective T2DM prevention.
- Program intensity matters. The most successful interventions to date have been those with a greater number of contact occasions for individualised diet and exercise coaching.
- Providing advice about future risk of T2DM to women with GDM has often 'fallen between the cracks' as this task is not 'owned' by any specific professional group. The growing evidence of effectiveness now justifies governments and health planners allocating funding and staff to implement universal post-partum screening and diabetes prevention programs for women with prior GDM to prevent or delay diabetes and save future healthcare costs. Ideally these would include system-level mechanisms to ensure all women are alerted to their ongoing risk and encouraged to follow diabetes prevention advice including participating in lifestyle intervention programs where these exist.
- Barriers identified to participation in diabetes prevention programs by new mothers, such as provision of childcare to enable mothers to participate in face-to-face programs, and/use of text, phone and Internet to make programs accessible to women with small children and working mothers, need to be addressed.
- Diets with higher nutritional quality are associated with smaller prospective weight gain, and lower rates of subsequent T2DM than poor quality diets.
- High glycaemic index (GI) diets are associated with increased risk of T2DM. Low-GI diets are associated with lower risk [9]. Glycaemic load (GL) is important, so it is prudent for women with prior GDM to be careful of overall quantity and daily distribution of carbohydrate consumed.

H.M. Taylor · C.E. Collins (✉)
Priority Research Centre in Physical Activity and Nutrition, School of Health Sciences,
University of Newcastle, Callaghan, NSW, Australia
e-mail: Clare.Collins@newcastle.edu.au

H.M. Taylor
e-mail: Helen.M.Taylor@uon.edu.au

L. MacDonald-Wicks · C.E. Collins
Nutrition and Dietetics, School of Health Sciences, Faculty of Health and Medicine,
University of Newcastle, Callaghan, NSW, Australia
e-mail: Lesley.Wicks@newcastle.edu.au

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_25

- As well as consuming lower total fat, the quality of dietary fats is important. Saturated fats should be minimised, and replaced by the 'healthier' mono- and polyunsaturated, for example, the Mediterranean diet pattern encouraged in the St. Carlos Gestational Study [10] in which the main sources of fat are olive oil, nuts, avocado and oily fish (Fig. 25.1).
- The style of diet in Fig. 25.2 has been shown to be effective for preventing T2DM in two randomised controlled trials, PREDIMED [11] and St Carlos [10]. The St Carlos Gestational Study was specific to women with GDM

Keywords Post-partum · Lifestyle intervention · Diet quality · Dietary patterns · Type 2 diabetes · Prevention · Glycaemic load · Mediterranean diet · Olive oil · Nuts

Abbreviations

GDM	Gestational diabetes mellitus
T2DM	Type 2 diabetes mellitus
GI	Glycaemic index
GL	Glycaemic load
DPP	Diabetes prevention program

Introduction

GDM identifies a predisposition to type 2 diabetes (T2DM). Affected women have a sevenfold risk of subsequently developing T2DM [12] and an estimated lifetime risk of up to 70%. Up to a third of parous women with T2DM have been diagnosed with GDM previously [13]. Proportions vary by population [14] with some groups at higher risk. For example, an estimated 50% of Hispanic women

Dietary issues for preventing progression to T2DM supported by Evidence:

1. **Diet Quality matters**: Worldwide there are culturally specific dietary guidelines for preventing chronic disease. **E**ating in alignment with your own or another country's dietary guidelines ensures a high quality diet that helps prevent obesity and type 2 diabetes.

2. **Preventing weight gain and losing excess weight matters**: Women in the reproductive age groups do not have optimal diets so personalised advice is warranted as a public health issue

3. **Glycaemic Load Matters**: Avoiding a high glycaemic load by choosing moderate quantities of low GI foods and avoiding high GI foods helps to prevent obesity and type 2 diabetes.

4. **Type of dietary Fat Matters:** Minimising saturated fats (animal fats and hard fats) and instead eating foods containing mono- and poly-unsaturated fatty acids (oily fish, olive oil, nuts) helps to prevent type 2 diabetes and cardiovascular disease.

Fig. 25.1 Dietary issues for preventing progression to T2DM supported by evidence

Example of dietary advice supported by RCT evidence for women with prior GDM:

- Weight loss is the priority for lowering future T2DM risk, in those currently overweight or obese(5).
- ANY nutritionally-sound weight loss diet that works for the individual is supported – choose a weight loss diet style that you can keep to long term.
- Try a Mediterranean style diet, that is largely plant-based including vegetables, fruits, legumes, nuts, extra virgin olive oil, oily fish, poultry, eggs and limited amounts of lean meats(9);
- Avoid high GI foods such as confectionery, cakes and biscuits (cookies), other white flour products, potatoes, sugar-sweetened beverages. Instead eat Low GI foods such as nuts, olives, legumes, fruits, whole grain foods (11);
- Avoid sugar-sweetened beverages(12, 13)
- Avoid saturated fats (eg Fatty meat, manufactured meat products, fast foods, cakes, cookies, high fat desserts, baked and fried snack foods). Use virgin olive oil and nuts to help to satisfy appetite.
- As well as selecting naturally Low GI foods, keep carbohydrate *quantity* low to moderate to prevent postprandial blood glucose spikes. Women who have followed a carbohydrate-modified diet to control their blood glucose levels during their GDM will be familiar with this style of eating.

Fig. 25.2 Example of dietary advice supported by RCT evidence for women with prior GDM

develop T2DM within 5 years of a GDM diagnosis [15]. England et al. [16] summarised the outcomes of a review by the USA Centres for Disease Control (CDC). This included an evidence review by an expert panel who concluded that women with prior GDM, even if normoglycaemic post-pregnancy, have the same level of risk of T2DM as people with pre-diabetes and should be included in diabetes prevention interventions. They also noted that GDM identifies women who will benefit from diabetes prevention interventions at an earlier stage of beta cell decline than would otherwise be possible in the absence of universal regular blood glucose screening [16].

There is a strong relationship between obesity and T2DM. In a large USA epidemiological study, adults with a BMI > 40 had a sevenfold increased risk of being diagnosed with diabetes (OR: 7.37, 95% confidence interval [CI], 6.39–8.50) [9]. Sustained weight gain increases diabetes risk, while weight loss decreases risk [17–19].

Three major diabetes prevention trials in Finland, China and the USA confirmed that programs to prevent diabetes using lifestyle interventions are both feasible and effective. The USA's Diabetes Prevention Program (DPP) achieved a 58% reduced risk of diabetes in people who achieved 7% reduction in weight in a well-resourced trial that provided individualised diet and lifestyle coaching and free access to exercise facilities [5]. The authors concluded that efforts to prevent T2DM should focus on weight loss and should include increasing physical activity. Weight loss is, therefore, a useful intermediate goal in research and evaluation of diabetes prevention programs.

Following a systematic review of the cost-effectiveness of diabetes interventions in 2010, the USA Centers for Disease Control (CDC) classified prevention of T2DM in women with a history of gestational diabetes as ***very cost-effective*** [7]. Even *delaying* the onset of T2DM is a worthwhile goal. For example, it has been calculated that if prevention programs delayed onset of T2DM by 6 years, with diabetes then treated appropriately, sight-threatening retinopathy would be reduced by 65% [20].

Some of the risk factors for future T2DM such as age and genetic predisposition are not modifiable, but physical activity and nutrition habits are, hence their importance.

Weight loss and maintenance of a healthy weight are key to reducing T2DM risk in at-risk individuals [3–6, 21, 22], including for women with prior GDM [6, 22]. Fundamentally, weight gain leading to overweight and obesity is due to dietary energy intake exceeding energy output. However, there are specific dietary patterns associated with an increased risk of obesity and T2DM in those who are genetically predisposed (see later).

This chapter addresses the nutrition part of the duo of healthy lifestyle habits. It focuses on the role of diet quality following GDM, and considers the relationship between diet quality, weight gain and obesity, as well as the specific effects of dietary patterns on glucose tolerance and risk of T2DM in women.

Main Text

There are two key dietary issues to consider for women with past GDM wishing to prevent or delay the onset of T2DM. First, there is the issue of weight management, which is dependent on energy balance: the difference between the energy intake (food and drink consumed) compared with energy expended (basal metabolic rate plus Physical activity). Second, we need to consider the effect of foods on metabolic processes. Quantity and types of carbohydrate foods are clearly important, as are the quantity and types of dietary fats.

Weight and Weight Loss in Relation to Women and GDM

Intervention Intensity Matters

In a review of success factors in real-world diabetes prevention interventions over the last 15 years, Aziz et al. [8] identified that weight loss outcomes were largely dependent on program intensity. However, many people at risk of diabetes do not get the opportunity to be involved in intensive programs, and Aziz makes the point that on a population basis, even small changes in weight due to participating in low-intensity programs that reach many people can still have considerable impact.

Obesity raises women's risk for GDM and T2DM, and for cardiovascular disease, hypertension, stroke, osteoarthritis, gallstones, endometrial, breast and colon cancers, fatty liver, obstructive sleep apnoea and urinary tract infections [23]. Because obesity is now prevalent in the reproductive-aged population (e.g. In Australia 42% of women aged 25–34 are overweight or obese [24]), many women who develop GDM are overweight or obese before pregnancy. In the CARDIA cohort, women with GDM were significantly heavier before pregnancy than other women [25]. Once they have had GDM, the risk of worsening glucose tolerance, developing T2DM or having another pregnancy affected by GDM is elevated, particularly if they retain excess weight, hence the importance of weight loss for women after a GDM pregnancy [5, 6, 25, 26], and before the next pregnancy, preferably to a BMI less than 25 [27].

Although absent from routine obstetric practice in recent years, regular weighing and encouragement of women to keep within recommended pregnancy weight gain targets has been acknowledged as very important in the 2009 IOM guidelines [27].

Results from the three major diabetes prevention trials confirmed the importance of weight loss for diabetes risk reduction [3–5, 28]. Weight loss therefore serves as a proxy measure of reduced T2DM risk and is a common measure of risk reduction in short trials that are not long enough to use incidence of T2DM as the outcome measure.

Obesity and pregnancy both increase insulin resistance [29], explaining why both conditions can trigger glucose intolerance in those with a genetic (or epigenetic) predisposition to T2DM. Epigenetics is the name given to changes in gene expression, brought about by nutrition or environmental exposures in the foetal and early life stage. Epigenetic influences mean the offspring of women with uncontrolled GDM are at lifelong risk of adverse metabolic characteristics, such as weight gain, early obesity and T2DM [30] (see Chap. 31).

For the majority of women post-GDM, excess weight gain is an important modifiable risk factor for T2DM. Due to the global obesity 'epidemic' it is probable that, in the absence of widespread and sustained participation in diabetes prevention programs, the majority of women with prior GDM will eventually develop T2DM.

In a cohort study of 1263 GDM-affected women, pre-pregnancy obesity and excessive pregnancy weight gain were associated with increased risk of pre-diabetes or T2DM one to five years post-partum [31]. A randomised controlled trial from Spain (The St. Carlos Gestational study) [32] confirmed that a high pre-pregnancy BMI and excess weight gain in early pregnancy are the major potentially modifiable risk factors for GDM.

The Diet, Exercise and Breastfeeding Intervention (DEBI) Trial in the USA was a DPP-style randomised controlled trial (RCT) in which 96 women with GDM were randomised to receive the intervention and 101 were randomised to usual care in Northern California [22]. This trial demonstrated that an intervention focussing on weight management, using a reduced fat energy restricted diet, breastfeeding and increased physical activity commencing at GDM diagnosis and continuing post-partum, significantly reduced fasting blood glucose levels measured 12 months post-partum.

In a study highlighting the effectiveness of intensity for weight loss interventions after GDM, O'Toole et al. [33] conducted a RCT in which 43 women were randomised to an intensive structured program or self-directed control group. The control group received just one hour of diet and exercise education and some printed resources. Women in the intervention group attended group sessions for 12 weeks, had individualised diet and exercise counselling, and kept food and activity diaries. They lost a mean of 7.3 kg over the year of follow-up, compared with a mean of 1.4 kg in the control group. Limitations of the study were its small size and the loss of nearly half of the participants to follow-up over the year, with only 23 of the 40 remaining. The authors concluded that future research should investigate barriers unique to the post-partum period. Other researchers have reported similar problems; Infanti et al. [34] reported accessibility, affordability and practicality as barriers to participation in a diabetes prevention trial in women with prior GDM and concluded that future programs, as well as addressing these barriers, should also focus on alleviating womens' concerns about long-term diabetes management.

Measuring Diet Quality

The term 'diet quality' refers to the nutritional quality of an individual's usual food intake in relation to health or physiological needs. As these vary across the population, there can be no single diet or food rated as optimal for everyone. Furthermore, perceptions of diet quality change over time as research uncovers 'new' metabolic functions for food components. Nutrient density is a useful measure of diet quality, particularly in terms of meeting nutrient requirements without having excessive total energy.

Research to date has commonly used percentages of energy from fat, protein and carbohydrate to describe diet quality. This practice has limitations as two diets can have the same percentages of energy from fat, but if one was lower in saturated fat, it would be rated as being of higher nutritional quality. Similarly, two diets may have the same percentages of energy from carbohydrate but not all carbohydrates have the same physiological properties. Compared with high glycaemic index (GI—see later) foods such as white flour products and potato, lower GI carbohydrate foods (e.g. wholegrains, oats, legumes, sweet potato), provide a slower rise in blood glucose compared with a similar amount of carbohydrate with a high GI. Replacing high-GI foods with those of a lower GI has benefits for control of blood glucose levels in people with diabetes [35] and has been reported to improve weight loss and glucose tolerance in women with prior GDM [35, 36].

The limitations of a sole focus on macronutrient percentages for describing diet quality have led to the development of specific measurement tools to capture overall diet quality. These 'diet quality indices' measure how closely dietary patterns align with national dietary guidelines. For example, the Australian Recommended Food Score (ARFS) measures how closely diets align with the Australian Dietary Guidelines [37], while the Healthy Eating Index relates to USA guidelines [38]. There is no perfect diet quality index or measurement tool for all cultures, language groups and food supplies. Different tools suit different research questions in different cultures. Guides for researchers to a variety of validated tools have been created by the public health authorities in the USA and UK and can be accessed online [39, 40].

Diet Quality, Weight and Diabetes Risk

Poor quality diets contribute to obesity, and hence contribute to the increased prevalence of GDM and T2DM. A recent systematic review investigating diet quality and weight change over time, demonstrated that diet quality indices better predict weight gain than other descriptors of diet quality, such as percentage of energy from macronutrients [41] and that higher quality diets are associated with less weight gain over time compared to poorer quality diets [41].

Aside from energy balance, there are several different aspects of diet quality relevant to prevention and treatment of GDM and T2DM. These include overall nutritional adequacy (including micronutrients and antioxidants), fibre, GI, GL, types of fat and ratio of protein to non-protein energy.

Evidence Specifically Regarding Diet in Pregnancy and Women with Current or Past GDM

Dietary treatment during GDM and T2DM has a common goal of keeping blood glucose as close to the normal range as possible. It is logical to assume that similar dietary principles will minimise risk of hyperglycaemia for women in the stage between GDM and T2DM. It follows that diets that help to prevent or delay onset of T2DM are likely to be similar to the diets prescribed for treatment of T2DM, including controlling the quantity, timing and glycaemic index of food choices. As well, evidence is mounting that, independently of weight management, the type of fat consumed is important, see below. (Fig. 25.1)

Mediterranean Diet RCTs

Recently published work has demonstrated that a largely plant-based Mediterranean style diet, with an overall low GI and with legumes, seeds and nuts is associated with one-fifth of the risk of T2DM compared with typical modern Western style eating habits.

The St Carlos Gestational study in Madrid [32] used a validated semi-quantitative food frequency questionnaire (FFQ) to measure eating patterns in early pregnancy. After controlling for BMI and the non-modifiable risk factors, such as age and family history, four patterns of eating were identified which collectively formed a *high-risk eating style*. These four higher risk eating patterns were regular consumption of: (1) Juices and sweetened drinks; (2) Pastries and cookies; (3) High glycaemic load refined cereals like rice, pasta and white breads; and (4) A low consumption of nuts.

Compared with women displaying none of these eating patterns, women with three or four high-risk eating patterns had a fivefold greater risk of developing GDM during their pregnancy. The data suggest that the opposite pattern, i.e. consumption of *very low or no* juice and sweet drinks, pastries and cookies, high-GI refined cereals like rice and white flour products, and with a *high intake of nuts* was associated with a lower risk of developing GDM (OR: 0.2 (0.07–0.62) (p = 0.00)).

It follows from these results that the dietitians who educate women during GDM should explain the ongoing risk of T2DM and empower women to make dietary improvements during pregnancy that they can live with in the long term.

The PREDIMED trial [11, 42] was a randomised cardiovascular disease primary prevention trial involving 7216 Spanish men and women aged 55–80 randomised to one of three dietary styles. All groups were expected to continue with their traditional Mediterranean style diets with the following modifications: Members of the control group received general low-fat dietary advice; the olive oil group (ME + EVOO) received 1 Litre of extra virgin olive oil per person per week; while the nuts group (MeDiet + nuts) received 30 g nuts per day instead. Annual dietary assessments using validated FFQs were performed. Results to date indicate that Mediterranean diet with either EVOO or nuts was associated with lower incidence of cardiovascular events and T2DM. The hazard ratios for incident T2DM compared with the control arm were 0.60 for extra olive oil (95% CI: 0.43, 0.85) and 0.82 for extra nuts (95% CI: 0.61, 1.10). Compared with those who consumed no nuts, consuming nuts three times a week was associated with 39% reduction in mortality risk. [11, 42]. These results were obtained in the absence of specific advice regarding caloric restriction.

Quantity and Type of Carbohydrate—Glycaemic Index Studies

GI is a ranking of carbohydrate in foods according to the relative rise in blood glucose levels after consumption, compared to an equivalent amount of carbohydrate consumed as glucose. Carbohydrate foods with a GI value of 55 or less are considered to have a low GI due to slower digestion, absorption and metabolism. This leads to a lower and slower rise in blood glucose and, therefore insulin levels. GL relates to the total glycaemic response so takes into account the quantity eaten as well as its GI.

In a small (n = 47) Canadian study in women diagnosed with GDM, women randomly allocated to follow a low-GI diet from 28 weeks gestation to birth had a greater proportion of fasting and post-prandial blood glucose results in the target ranges (3.8–5.2 mmol/L, and 5.0–6.6 mmol/L, respectively) than the control group. The study reported that women found low-GI foods acceptable and were willing to continue using them after their pregnancy [23].

In 2006, Moses et al. [43] reported on a small study (n = 62) in which pregnant women who did not have either GDM nor T2DM were allocated to receive either 'high-fibre low-sugar' dietary advice or low-glycaemic index dietary advice. Compared with babies born to women following low-GI diets, babies born to women following the 'high-fibre low-sugar' (higher GI) diet were heavier (3408 ± 78 vs. 3644 ± 90 g; P = 0.051), had a higher ponderal index (2.62 ± 0.04 vs. 2.74 ± 0.04; P = 0.03) and a higher prevalence of large for gestational age (3.1% vs. 33.3% (P = 0.01)). After 2 years follow-up, when 9 of the 11 babies born large for gestational age (LGA) were reassessed, while not significantly taller, they were significantly heavier than the infants who were not LGA at birth (13.6 kg compared with 12.4 kg for the non-LGA babies [44].

In an extension to this study [45], 19 women originally randomised to the 'high-fibre low-sugar' (higher GI) diet met the criteria to commence insulin treatment. This was a significantly higher proportion than those in the low-GI diet group (19 of 32 (59%, p = 0.023)). Nine of these 19 women were able to avoid insulin use by changing to a low-glycaemic index diet. This result is consistent

with knowledge that there is a lower demand on endogenous insulin production in response to low-GI meals in people with T2DM [46]. The authors concluded that a low-GI diet offers a safe way to reduce the need for insulin in GDM without compromising obstetric outcomes [45].

The Best Evidence to Date for Women with Prior GDM—Reviews and RCTs

To date, relatively few RCTs have been conducted in women with prior GDM. Morton's 2014 systematic review [47] found that the majority of interventions were short duration pilot or feasibility studies with relatively small numbers of participants, with a wide variation in settings, populations, interventions, outcome measures and duration of follow-up. Given this heterogeneity, generalisations about effectiveness were difficult. However, they highlighted the likely protective effect of breast-feeding in reducing progression to type 2 diabetes.

Similarly, Chasan-Taber identified nine studies in a review published in 2015 [48]. Six included a dietary intervention, while three focussed on physical activity only. Only two were of long enough duration to evaluate the impact of lifestyle intervention on subsequent incidence of diabetes. All used intermediate outcome measures, such as weight loss and physical activity as proxy measures for decreasing risk.

The most successful trial to date was the well-resourced and intensive DPP in the USA. It included a subset of 350 women with self-reported prior GDM. Among this group, the incidence of T2DM was 7.4 per 100 person-years in the intervention group compared with 15.2 in the control group, a reduction of 53% ($p = 0.002$). A limitation of the study was that at the DPP baseline, the GDM-affected women were an average of 12 years on from their diagnosis of GDM, and they had not developed T2DM by that point. The highest risk period for women with prior GDM for developing T2DM is in the 5 years following initial diagnosis. Women who had already developed T2DM were ineligible for the DPP trial, hence the authors were unable to report on the impact the program might have on incidence of T2DM if the intervention had been initiated immediately post-partum. Other RCTs have been shorter and less intensive but in all trials, the results have been promising, with all changes in measures being in the favourable direction.

Guo et al. (2016) conducted a similar systematic review which found an additional three published trials [49] and a further paper has been published since the Guo et al. review. Of the 11 trials, Guo et al. identified that demonstrated an effect on key outcomes (incident T2DM, weight-related variables or insulin resistance measures), nine included a dietary intervention and six of these used dietitians to provide the intervention. Intensity, measured as contact frequency, varied from monthly to biannually, with two interventions using phone call contact in place of face-to-face visits, in an attempt to replicate the successes of the DPP trial with fewer resources. The DPP utilised weekly face-to-face lifestyle coaching by case managers trained to deliver dietary education components developed by dietitian-nutritionists.

The results of a post-partum RCT in Madrid [10] were published recently. The study used a lifestyle intervention based on the Mediterranean diet (see below) and supervised exercise sessions. Follow-up was at 3, 6, 12 and 24 months, during which there was reinforcement education at each visit. The control arm received the same initial group dietary education, but was followed up by their family physician, except for annual follow-up appointment with the research team. The dietary pattern recommended to *all* the women was the Mediterranean diet pattern, specifically:

> 5 or more serves of fruits and vegetables per day, legumes at least twice a week, nuts at least three times a week, more than 40 ml per day of virgin olive oil, three or more serves of oily fish per week, less than 2 serves of red and processed meats per week, and less than 2 serves per week of non-skim dairy products.

The goal was to achieve a score of five or greater on the nutrition score described in the Diabetes Nutrition and Complications Trial (DNCT) [50, 51]. In this Spanish population (with an expected progression to T2DM of 50% over 5 years), there was a 35% reduction in progression to T2DM in the intervention group, BMI, waist circumference, fasting plasma insulin levels, HOMA-IR, triglycerides, LDL-cholesterol and apo lipoprotein B were all significantly reduced in the intervention group ($p \leq 0.0.05$) compared with the control group. Increased body weight and an unhealthy dietary fat intake were most predictive of T2DM diagnosis within the three-year trial.

As well as confirming previous findings that intensity of professional support is important to success in lifestyle interventions to reduce risk of diabetes, these studies offer support for a Mediterranean style diet that includes virgin olive oil, nuts or both, as a diet lowering the risk of T2DM in people at risk.

Discussion and Recommendations for Practice

Multiple reviews of dietary strategies to prevent T2DM have concluded that a single 'best' dietary pattern does not exist. Rather a prudent dietary pattern is optimal, and this varies across countries and across national dietary guidelines. The Mediterranean style diet offers many advantages not least of which is that many people find it palatable so it may be easier to adhere to than other diet styles. It appears that low-GI diets reduce demand on endogenous insulin. Analysis of micronutrient content and cost effectiveness indicate that a low-GI diet may improve nutrient density without significant cost increase to clients [52].

The nuances of the best dietary advice for women with prior GDM appear less important than the achievement of weight reduction. *Adherence* to *any* sensible dietary plan (e.g. low carbohydrate, low GI, low fat) that facilitates weight reduction has been shown to be the key issue rather than the macronutrient composition. Several reviewers of dietary strategies have concluded that health professionals should be flexible in supporting the individual to keep to whatever style of weight reducing diet they are able to adhere to, and this principle is stated explicitly in the Diabetes UK Dietary Guidelines [53].

Providing dietary counselling is one of the multiple strategies that needs to be implemented simultaneously, so this summary touches on a few related areas, in particular arrangements of services within healthcare systems for connecting women with the motivation, knowledge and empowerment they need if they are to delay or prevent T2DM.

In a letter to the Editor of the journal Diabetes Research & Clinical Practice, Kalra, Gupta and Kalra (2015) suggested a simple mnemonic summarising five components of postnatal care for women with GDM: ABCDE which stands for **A**ssessment (regular follow-up), **B**reastfeeding, **C**ontraception, **D**ietary modification and **E**xercise (Physical Activity) [54]. The authors explain that the inclusion of contraception highlights the importance of partner/family involvement. As well, Kjos has previously recommended contraception be used by women with prior GDM in case they become pregnant while unknowingly hyperglycaemic, which increases risk of birth defects [14]. A third reason to recommend contraception is to space pregnancies to provide opportunity to lose excess weight gained during pregnancy before commencing the next pregnancy.

As well as increasing mother–baby bonding, reducing risk of infections, and helping maternal weight loss, there is growing evidence that breastfeeding reduces the risk of obesity, independently of weight loss, and reduces the risk of T2DM in the mother and potentially the child [55, 56]. Encouraging women with GDM to commence and maintain breastfeeding is particularly important because of its potential contribution as one of the strategies that will help to interrupt the cross-generational increase in T2DM. For more information on breastfeeding refer to Chaps. 18 and 28 .

Given the association between obesity and GDM, prevention of T2DM would ideally begin with pre-conception weight loss for women who are obese or who have family history of diabetes or other diabetes risk factors, to minimise risk of GDM developing.

The DEBI trial provides evidence that a T2DM prevention intervention that begins during GDM pregnancy may offer advantages over commencing interventions post-partum when mothers are coping with the demands of a new baby.

Morrison et al. [57] previously reported that women are often not fully aware of their ongoing risk for T2DM following GDM. Advising women of this ongoing risk is a duty that commonly 'slips through the cracks' in healthcare systems, because no group of healthcare workers is specifically ascribed this duty. It would therefore be helpful if care pathways for women after GDM included prompts for *all* health professionals to refer women post-GDM to either a structured DPP or dietitian, and ideally for a *set* of sessions over 6-12 months given the demonstrated importance of intensity of contacts for weight loss. There is evidence that many women with prior GDM would welcome this continuity of care post-pregnancy, and would particularly appreciate help with managing post-partum weight retention [57].

Health Funding and Planning Implications

The most successful lifestyle interventions have utilised individualised professional advice and lifestyle coaching. The DPP and the Finnish Diabetes Prevention Study set the success benchmark that other less intensive programs have struggled to achieve. Despite being resource-intensive, these programs are *very cost-effective* [7]. Given the lifelong burden diabetes places on individuals and increasingly on health budgets, it would be prudent for governments and health funders to compare the costs of providing programs with the long-term costs of NOT providing such programs.

Conclusions

A challenge for governments and healthcare planners is to work together to identify the best set of policies and programs that can be implemented at scale, to ensure all women with prior GDM have ongoing opportunities to access prevention programs and/or regular contact with a dietitian. In addition, ongoing research will need to identify effective and affordable ways to deliver diet and exercise coaching for diabetes prevention using technology including telephone, text messaging, Internet and social media, to make these intervention programs more accessible to working mothers and mothers with small children by addressing common barriers of time, cost, travel, location and childcare.

This chapter has examined diet after GDM looking specifically at how it can be modified to prevent T2DM. It is clear that for women who are predisposed to GDM and T2DM, the key nutritional issues are weight management and diet quality. Alongside exercise, a high nutritional quality diet, mostly plant based with legumes nuts, oily fish, vegetables and olive oil providing a larger proportion of the diet than, is typical in developed countries and assists in preventing obesity, GDM, T2DM and cardiovascular disease. If we are to reduce future diabetes and future healthcare costs, we need to persuade people on a population level to replace the high-fat high-sugar modern diet with this more healthy way of eating, and pass this habit on to their at-risk children for a healthier future.

References

1. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773–9.
2. Lillycrop KA, Burdge GC. Epigenetic mechanisms linking early nutrition to long term health. Baillieres Best Pract Res Clin Endocrinol Metab. 2012;26(5):667–76.
3. Pan X-R, Li G-W, Hu Y-H, Wang J-X, Yang W-Y, An Z-X, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study. Diabetes Care. 1997;20(4):537–44.
4. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343–50.
5. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New Engl J Med. 2002;346(6):393–403.
6. Ratner R, Christophi C, Metzger B, Dabelea D, Bennett P, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93(12):4774–9.
7. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010;33(8):1872–94.
8. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. Implement Sci. 2015;10(1):172.
9. Dong JY, Zhang L, Zhang YH, Qin LQ. Dietary glycaemic index and glycaemic load in relation to the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Br J Nutr. 2011;106(11):1649–54.
10. Pérez-Ferre N, Del Valle L, Torrejón MJ, Barca I, Calvo MI, Matía P, et al. Diabetes mellitus and abnormal glucose tolerance development after gestational diabetes: a three-year, prospective, randomized, clinical-based, Mediterranean lifestyle interventional study with parallel groups. Clin Nutr. 2015;34(4):579–85, 7p.
11. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 2011;34(1):14–9.
12. Bellamy CJ-P, Hingorani AD, Williams W. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373:1773–9.
13. Cheung NWBK. Population health significance of gestational diabetes. Diabetes Care. 2003;26(7):2005–9.
14. Kjos SL. After pregnancy complicated by diabetes: postpartum care and education. Obstet Gynecol Clin North Am. 2007;34(2):335–49, x.
15. Chasan-Taber L, Marcus BH, Rosal MC, Tucker KL, Hartman SJ, Pekow P, et al. Estudio Parto: postpartum diabetes prevention program for hispanic women with abnormal glucose tolerance in pregnancy: a randomised controlled trial—study protocol. BMC Pregnancy Childbirth. 2014;14:100.
16. England LJ, Dietz PM, Njoroge T, Callaghan WM, Bruce C, Buus RM, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. Am J Obstet Gynecol. 2009;200(4):365, e1–e8.
17. Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. DIetary fiber, glycemic load, and risk of non—insulin-dependent diabetes mellitus in women. JAMA. 1997;277(6):472–7.
18. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ. 2015;351.
19. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care. 2010;33(11):2477–83.
20. Eastman RC, Silverman R, Harris M, Javitt JC, Chiang YP, Gorden P. Lessening the burden of diabetes. Intervention strategies. Diabetes Care. 1993;16(8):1095–102.
21. Bennett WL, Liu SH, Yeh HC, Nicholson WK, Gunderson EP, Lewis CE, et al. Association of gestational diabetes mellitus with weight and preventive health behaviors after pregnancy: the CARDIA study. Diabetes. 2012;61:A639.
22. Ehrlich SF, Hedderson MM, Feng J, Crites Y, Quesenberry CP, Ferrara A. Lifestyle intervention improves postpartum fasting glucose levels in women with gestational diabetes. Diabetes. 2014;63:A95.
23. Grant SM, Wolever TM, O'Connor DL, Nisenbaum R, Josse RG. Effect of a low glycaemic index diet on blood glucose in women with gestational hyperglycaemia. Diabetes Res Clin Pract. 2011;91(1):15–22.
24. Australian_Bureau_of_Statistics. Ausstats: Australian Health Statistics (Government Health Statistics). 2012 (updated 17/3/2016; cited 2016 17 March). Available from: www.abs.gov.au/ausstats/abs@nfs/Lookup/034947E844F25207AA39914BDC7?opendocument.

25. Bennett WL, Liu S-H, Yeh H-C, Nicholson WK, Gunderson EP, Lewis CE, et al. Changes in weight and health behaviors after pregnancies complicated by gestational diabetes mellitus: the CARDIA study. Obesity (Silver Spring). 2013;21(6):1269–75.
26. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of body mass index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health. 2007;7(1):1–8.
27. Rasmussen K, Medicine_of_the_National_Academies. Io. Weight gain during pregnancy: reexamining the guidelines. Washington, D.C.: Institute of Medicine of the National Academies. 2009.
28. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102–7.
29. Catalano P, Kirwan JP, Haugel-de Mouzonz S, Kingzz J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. J Nutr. 2003;133:1674S–83S.
30. van Dijk SJ, Tellam RL, Morrison JL, Muhlhausler BS, Molloy PL. Recent developments on the role of epigenetics in obesity and metabolic disease. Clin Epigenetics. 2015;7(1).
31. Liu H, Zhang C, Zhang S, Wang L, Leng J, Liu D, et al. Prepregnancy body mass index and weight change on postpartum diabetes risk among gestational diabetes women. Obesity (Silver Spring). 2014;22(6):1560–7.
32. Ruiz-Gracia T, Duran A, Fuentes M, Rubio M, Runkle I, Carrera E. Lifestyle patterns in early pregnancy linked to gestational diabetes mellitus diagnoses when IADPSG criteria. The St Carlos gestational study. Clin Nutr. In Press.
33. O'Toole M, Sawicki M, Artal R. Structured diet and physical activity prevent postpartum weight retention. J Womens Health (Larchmt). 2003;12(10):991–8.
34. Infanti JJ, O'Dea A, Gibson I, McGuire BE, Newell J, Glynn LG, et al. Reasons for participation and non-participation in a diabetes prevention trial among women with prior gestational diabetes mellitus (GDM). BMC Med Res Methodol. 2014;14:13.
35. Gutschall MD, Miller CK, Mitchell DC, Lawrence FR. A randomized behavioural trial targeting glycaemic index improves dietary, weight and metabolic outcomes in patients with type 2 diabetes. Public Health Nutr. 2009; 12(10):1846–54.
36. Shyam S, Arshad F, Abdul Ghani R, Wahab NA, Safii NS, Nisak MY, et al. Low glycaemic index diets improve glucose tolerance and body weight in women with previous history of gestational diabetes: a six months randomized trial. Nutr J. 2013;12:68.
37. Collins C, Burrows T, Rollo M, Boggess M, Watson J, Guest M, et al. The comparative validity and reproducibility of a diet quality index for adults: the Australian recommended food score. Nutrients. 2015;7(2):785–98.
38. Wirt A, Collins CE. Diet quality—what is it and does it matter? Public Health Nutr. 2009;12(12):2473–92.
39. Medical Research Council. Diet and physical activity measurement toolkit UK: Medical Research Council (UK); (cited 2016 19 January).
40. NIH National Cancer Institute USA. Dietary assessment primer, home page. National Institutes of Health, National Cancer Institute. (http://dietassessmentprimer.cancer.gov/). Accessed 19 Jan 2016.
41. Aljadani H, Patterson A, Sibbritt D, Collins CE. Diet quality and weight change in adults over time: a systematic review of cohort studies. Curr Nutr Rep. 2015;4(1):88–101.
42. Guasch-Ferré M, Bulló M, Martínez-González MÁ, Ros E, Corella D, Estruch R, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med. 2013;11:164.
43. Moses RG, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, et al. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 2006;84(4):807–12.
44. Moses RG, Luebke M, Petocz P, Brand-Miller JC. Maternal diet and infant size 2 y after the completion of a study of a low-glycemic-index diet in pregnancy. Am J Clin Nutr. 2007;86(6):1806.
45. Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial. Diabetes Care. 2009;32(6):996–1000, 5p.
46. Wolever T, Nguyen P, Chiasson J, Hunt J, Josse R, Palmason C, et al. Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. Am J Clin Nutr. 1994;59:1265–9.
47. Morton S, Kirkwood S, Thangaratinam S. Interventions to modify the progression to type 2 diabetes mellitus in women with gestational diabetes: a systematic review of literature. Curr Opin Obstet Gynecol. 2014;26(6):476–86.
48. Chasan-Taber L. Lifestyle interventions to reduce risk of diabetes among women with prior gestational diabetes mellitus. Best Pract Res Clin Obstet. Gynaecol. 2015;29(1):110–22.
49. Guo J, Chen JL, Whittemore R, Whitaker E. Postpartum lifestyle interventions to prevent type 2 diabetes among women with history of gestational diabetes: a systematic review of randomized clinical trials. J Womens Health (Larchmt). 2016;25(1):38–49.
50. Group. DaNS. Diabetes nutrition and complications trial (DNCT): food intake and targets of diabetes treatment in a sample of Spanish people with diabetes. Diabetes and Nutrition Study Group of the Spanish Diabetes Association (GSEDNu). Diabetes Care. 1997;20(7):1078–80.

51. Diabetes, Nutrition Study Group of the Spanish Diabetes A. Diabetes Nutrition and Complications Trial: adherence to the ADA nutritional recommendations, targets of metabolic control, and onset of diabetes complications. A 7-year, prospective, population-based, observational multicenter study. J Diab Complications. 2006;20(6):361–6.
52. Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2011;21(Suppl 2):B32–48.
53. Dyson PA, Kelly T, Deakin T, Duncan A, Frost G, Harrison Z, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. Diabetes Med. 2011;28(11):1282–8.
54. Kalra B, Gupta Y, Kalra S. Gestational diabetes mellitus (GDM) follow up: as simple as ABCDE. Diabetes Res Clin Pract. 2015;107(2):e5–6.
55. Gunderson EP, Hurston SR, Dewey KG, Faith MS, Charvat-Aguilar N, Khoury VC, et al. The study of women, infant feeding and type 2 diabetes after GDM pregnancy and growth of their offspring (SWIFT Offspring study): prospective design, methodology and baseline characteristics. BMC Pregnancy Childbirth. 2015;15:150.
56. Mayer-Davis EJ, Dabelea D, Lamichhane AP, D'Agostino RB Jr, Liese AD, Thomas J, et al. Breast-feeding and type 2 diabetes in the youth of three ethnic groups: the SEARCh for diabetes in youth case-control study. Diabetes Care. 2008;31(3):470–5.
57. Morrison MK, Lowe JM, Collins CE. Perceived risk of type 2 diabetes in Australian women with a recent history of gestational diabetes mellitus. Diabetes Med. 2010;27(8):882–6.

Chapter 26
Post-partum Oxidative Stress Markers in Women with Previous Gestational Diabetes in Relation to Vascular Damage

M.M. Roca-Rodríguez, C. López-Tinoco and M. Aguilar-Diosdado

Key Points

- Increased adhesion molecules may be the result of early vascular abnormalities in GDM and, therefore, represent a consequence rather than a potential cause of early vascular lesions.
- Oxidative stress may be responsible for maternal and fetal complications, and disruption of normal intrauterine programming leading to metabolic diseases in later life.
- There are no conclusive results and studies in the literature regarding the role of adipokines, oxidative stress, and AM levels in relation to vascular and metabolic changes in women with previous GDM.
- It is still unclear whether a diet rich in antioxidants, or antioxidant supplementation of the diet may improve oxidative stress.
- Measurement of hormonal, metabolic, and vascular changes occurring in GDM women during pregnancy and post-partum are important for early identification of those at high risk of vascular damage, and for implementation of intensive treatment strategies to avoid, or reduce, CVD.

Keywords Endothelial dysfunction · Oxidative stress · Gestational diabetes mellitus · Placenta · Post-partum

Abbreviations

GDM	Gestational diabetes mellitus
DMT2	Diabetes mellitus type 2
CVD	Cardiovascular diseases
MetS	Metabolic syndrome
CRP	C-reactive protein
TNF-α	Tumor necrosis factor alpha
IL-6	Interleukin 6
PAI-1	Plasminogen activator inhibitor 1

M.M. Roca-Rodríguez · C. López-Tinoco · M. Aguilar-Diosdado (✉)
Department of Endocrinology and Nutrition, Puerta del Mar University Hospital, Ana de Viya, 21, Cadiz, Spain
e-mail: manuel.aguilar.sspa@juntadeandalucia.es

M.M. Roca-Rodríguez
e-mail: maroca80@gmail.com

C. López-Tinoco
e-mail: cristinalopeztinoco@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_26

AMs	Adhesion molecules
ICAM-1	Intercellular adhesion molecule-1
VCAM-1	Vascular adhesion molecule-1
ROS	Reactive oxidative substances
NF-kB	Nuclear factor-kB
NO	Nitric oxide
LPO	Lipoperoxides
MDA	Malondialdehyde
TBARS	Thiobarbituric acid reactive substances
AOPPs	Oxidative protein products
hs-CRP	High-sensitivity C-reactive protein
TAC	Total antioxidant capacity
SOD	Superoxide dismutase
GPX	Glutathione peroxidase
GSH	Glutathione reductase
BMI	Body mass index
OGTT	Oral glucose tolerance test
AGE	Advanced glycoxidation endproduct

Introduction

Gestational Diabetes Mellitus and Metabolic Syndrome

Women with gestational diabetes mellitus (GDM) are at risk of developing type 2 diabetes (T2DM) and cardiovascular diseases (CVD) but the mechanisms underlying these processes are still unclear. Subclinical inflammation is considered the link between GDM and metabolic syndrome (MetS) through insulin resistance, and there are emerging biomarkers of MetS such as leptin, adiponectin, endothelial dysfunction, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), and fibrinogen. Some authors have reported higher levels of adhesion molecules (AMs) such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and cellular molecule (E-selectin), in women at risk of developing T2DM and in T1DM complications including retinopathy and nephropathy while some data suggest that the degree of glycemic control may influence AM concentrations via oxidative stress. Although high glucose-induced oxidative stress has been proposed as a mediator of endothelial damage in diabetes, there is no consensus regarding GDM and oxidant/antioxidant balance. Pregnancy could represent a precursor to an oxidative stress condition. In addition, it is still unclear whether a diet rich in antioxidants (or antioxidant supplementation of the diet) may improve oxidative stress in GDM, and prevent the subsequent development of T2DM [1].

Inflammation and Endothelial Damage in Women with Gestational Diabetes Mellitus

Epidemiological and experimental evidence exist demonstrating an association between markers of subclinical inflammation with metabolic diseases, obesity, T2DM, and GDM. Obesity is a critical risk-factor in the development of GDM. Evidence suggests that individuals at risk of developing

glucose intolerance, have fat-cell dysfunction resulting in excessive levels of pro-inflammatory adipokines (leptin, resistin, TNF-α and IL-6), insulin resistance, and lower anti-inflammatory adipokines and insulin sensitizers (adiponectin). Among these pro-inflammatory cytokines, TNF-α and leptin have been suggested as the strongest predictors of insulin resistance in T2DM [2]. Due to the similarity between T2DM and GDM and the clear relationship between T2DM and inflammation, the hypothesis is that inflammation, as well, could be implicated in the pathophysiology of GDM. GDM could be attributed to secretion of upregulated inflammatory cytokines from gestational tissues that accelerate insulin resistance.

TNF-α has been associated with insulin resistance during pregnancy. Kirwan et al. [3] reported that TNF-α concentrations were inversely related to insulin sensitivity, as measured in studies using euglycemic-hyperinsulinemic clamp. Further, compared with other hormones related to pregnancy (leptin, cortisol, placental lactogen, human chorionic gonadotropin, estradiol, progesterone, and prolactin), the variation in the levels of TNF-α pre- and post-pregnancy were the best predictors of insulin sensitivity. Winkler et al. [4] found an association between TNF-α and C-peptide levels in the fasting state. We [5] and others have reported increased TNF-α levels in GDM, but other investigators have not confirmed this association. IL-6 and IL-8 may also be involved in the pathogenesis of insulin resistance in T2DM. Moreover, the correlation between levels of IL-6 with adiposity appears to be greater than with TNF-α, and there is a direct correlation between insulin resistance and levels of IL-6. Contradictory results have been reported with respect to leptin in patients with GDM; while some investigators [6], including ourselves [5], found high levels in patients with GDM, others did not [7]. Adiponectin, an anti-inflammatory adipokine, is considered to have beneficial effects on insulin sensitivity. Adiponectin levels have been observed to be lower in pregnant women with GDM [5] compared to control individuals, and this finding has been associated with the pathogenesis of GDM (insulin resistance and beta cell dysfunction). A recent meta-analysis confirmed increased levels of TNF-α and leptin, and the decreased level of adiponectin, in GDM [8]. As such, this upregulation of pro-inflammatory mediators, and the downregulation of anti-inflammatory molecules, could lead to the development of chronic inflammatory state and to contribute to the hyperinsulinemia in GDM.

Cytokines may be involved in the endothelial damage that these women often develop later in life. The AMs are critical in the normal development and function of the heart and blood vessels, and have been implicated in the pathogenesis of CVD. The two molecules most closely associated with endothelial dysfunction resulting from inflammation are ICAM-1 and VCAM-1. Krauss et al. [9] presented evidence for potentially elevated ICAM-1 levels in women with GDM, while Kautsky-Willer et al. [10] demonstrated increased levels of VCAM-1 in women with GDM, and in pregnant women with normal glucose tolerance compared with non-pregnant control individuals. More recently, Mordwinkin et al. [11] observed that levels of VCAM-1 and ICAM-1 were both significantly higher in GDM patients compared to control. Hence, a link between TNF-α production, inflammation, and endothelial damage can be postulated. TNF-α and AMs have been shown to be increased in patients with diabetes mellitus, mainly in those with vascular complications. Whether or not the correlation observed between VCAM-1 and TNF-α during pregnancy in women with GDM is maintained later in life, especially in those women developing T2DM, has yet to be confirmed. Inflammation and AMs could be involved in the vascular complications occurring in women with glucose intolerance.

Oxidative Stress Markers in Women with Gestational Diabetes

Oxidative stress results from an imbalance between the increase in the formation of reactive oxidative substances (ROS) and the synthesis of antioxidative defense mechanisms. One current hypothesis is that oxidative stress, following the mechanisms associated with the production of superoxide, is a

pathogenic factor that leads to insulin resistance, β-cell dysfunction, glucose intolerance and, finally, to T2DM. ROS is implicated in regulating important physiological functions such as the activation of transcription factors; for example, nuclear factor-kB (NF-kB), which is recognized as the principal regulator of the genetic expression of stress response. NF-kB regulates the expression of multiple immunological and inflammatory genes, including the inflammatory cytokines, proteins, and enzymes implicated in the generation of ROS. The injurious effects of oxidative stress in the cardiovascular system are numerous and varied, but can be summarized as the reduction in the availability of nitric oxide (NO), increase in the inflammatory markers implicated in accelerated atherosclerosis, and modifications of lipids and lipoproteins [12].

Oxidative stress can play an important role not only in the pathogenesis of T2DM but also in GDM, and the development of mother–fetus complications. Associations between GDM and oxidative stress markers have been reported extensively [13–18]. We have demonstrated that women with GDM have elevated serum levels of lipoperoxides (LPO) [19]. Like us, several other investigators have shown associations between GDM and markers of oxidative stress during pregnancy [13–18, 20]. For example, maternal malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) levels in plasma have been described as being higher in GDM [13, 14]. In another study [17] MDA levels were higher in a GDM group, but advanced oxidative protein products (AOPPs) and LPO levels were unchanged in GDM relative to normal pregnancies. The most recent study [18] showed that levels of high-sensitivity C-reactive protein (hs-CRP) and high fluorescence reticulocytes at fasting, and hs-CRP in a 1 h OGTT, were significantly associated with GDM. Toescu et al. [16] in a prospective study that assessed changes in the lipid profile and oxidative stress markers in successive trimesters, observed that lipids and LPO levels were higher in each trimester in women with T2DM, T1DM, and GDM when compared to control subjects. The increased oxidative stress in GDM is attributed to increased levels of free radicals, and deficiencies in antioxidant defense systems [21]. The literature contains conflicting results on the expression and activity of antioxidants in GDM. Lower total antioxidant capacity (TAC) has been described in GDM [13–17] while several investigators have observed decreased levels of superoxide dismutase (SOD) [19, 20] in patients with GDM. However, in other studies, SOD levels were reported as being increased in women with GDM [22]. We [19], as well as Madazli et al. [20], have shown that the levels of catalase were decreased in the patients with GDM. These results differ from other studies in which nonsignificant differences had been described [15]. Decreased [13] as well as increased levels [21] of glutathione peroxidase (GPX) have been described in GDM patients. These data suggest that the increase in oxidative stress and the decrease in the antioxidant defense can be implicated in the progression and/or pathology of GDM. These findings have been detected in a few studies (and with reduced sample size); the most relevant are shown in Table 26.1.

It is possible that maternal diabetes during pregnancy may induce oxidative stress in the newborn. Markers of reactive oxidative species are increased in diabetic pregnancies, and MDA and glutathione reductase (GSH) levels are increased in cord plasma [23]. The macrosomic offspring of women with GDM have enhanced TBARS levels while, on the other hand, antioxidants have been reported as unchanged, higher, or lower in cord blood from diabetic women. Cord plasma catalase, GPX, SOD, and TAC activities are significantly decreased in GDM [23]. Related to the impact of oxidative environment on fetus, it has been suggested that placenta responds with a higher expression of antioxidant enzymes that could alleviate the effect of systemic elevation of ROS (Fig. 26.1) [24]. Oxidative stress effects of the mode of delivery of the fetus appear not to be conclusive. Radjl et al. [14] demonstrated higher SOD activities post-partum in diabetic mothers undergoing cesarean section while, in another study, the levels of LPO were elevated and the GPX decreased in those females who had had a cesarean delivery [11]. An explanation could be because of a greater oxidative capacity and lower antioxidative status in GDM.

Table 26.1 Summary of the data published on markers of oxidative stress and antioxidants in females with GDM compared to control individuals without GDM

Study (ref.)	DMG/control N	Weeks of gestation	Oxidative stress markers	Results: GDM versus control
Peuchant [21]	16/27	3rd trimester	MDA, SOD, GPX, vitamins A and E	MDA increased, GPX decreased, others NS
Chaudhari [22]	20/20	3rd trimester	MDA, SOD, CAT	MDA increased, SOD decreased, CAT NS
Radjl [23]	6/18	Pre-partum	SOD, GPX, GSH, TBARS, TAC, LDLox and anti-LDLox antibody	TBARS increased, GSH decreased
Orhan [24]	3/16	3rd trimester	GPX, GSH, GST TBARS, CAT, MDA	All NS
Toescu [25]	12/17	1st, 2nd and 3rd trimester	TAC, LPO	TAC decreased, LPO NS
Karacay [26]	27/29	2nd and 3rd trimester	TAC, MDA, AOPPs, LHP	TAC decreased, MDA increased, others NS
Zhu [27]	36/36	2nd and 3rd trimester	hs-CRP, CER, NT	hs-CRP increased, CER, NT NS
López-Tinoco [28]	53/25	2nd and 3rd trimester	LPO, CAT, SOD, GPX, GSH, GST	LPO increased, CAT, SOD, GPX decreased

GDM gestational diabetes mellitus; *MDA* malondialdehyde; *SOD* superoxide dismutase; *CAT* catalase; *GPX* glutathione peroxidase; *GSH* glutathione reductase; *GST* glutathione transferase; *TBARS* thiobarbituric acid reactive substance; *TAC* total antioxidant capacity; *LPO* lipoperoxide; *AOPPs* protein oxidation markers; *MPO* myeloperoxidase; *LHP* lipid hydroperoxide; *hs-CRP* high-sensitivity C-reactive protein; *CER* ceruloplasmin; *NT* nitrotyrosine

Post-partum Inflammation and Endothelial Damage in Women with Previous GDM

We have observed that women with previous GDM had central trunk adiposity, carbohydrate intolerance, and adverse adipokine profile; all of which are risk factors for future development of CVD [25]. The prevalence of MetS in the post-partum period in our patients was higher than previous published data (14.6–22% vs. 9%) [26]. A recent meta-analysis [27] showed a fourfold increased risk of developing MetS in women with a history of GDM. We found that pre-pregnancy obesity was an independent risk factor in the development of GDM and carbohydrate intolerance in the post-partum period, and that women with prior GDM had higher risk of MetS when they had a higher BMI [5, 25]. Sokup et al. [28] found that baseline triglyceride levels are a CVD risk marker. Also, triglyceride concentrations are a pathophysiological parameter independently associated with endothelial dysfunction in nondiabetic women with previous GDM at 2-24 months after an index pregnancy. Hence, normalization of triglycerides should be included in preventive therapy after a pregnancy complicated by GDM. In contrast, we found no statistically significant differences in lipoprotein profiles [25].

Uric acid is a marker of inflammation. It has not been well studied despite its potential involvement in endothelial dysfunction and generalized atherosclerosis. In line with other investigators [29], we found high uric acid levels in women with previous GDM [25].

Adipose tissue plays an important role in the regulation of insulin sensitivity. We had noted [25] that plasma concentrations of TNF-α, IL-6 and adiponectin were similar in women with and without a history of GDM (Table 26.2) while, conversely, plasma leptin levels were higher in cases in the post-partum period. These results are similar to some studies that found no difference between groups

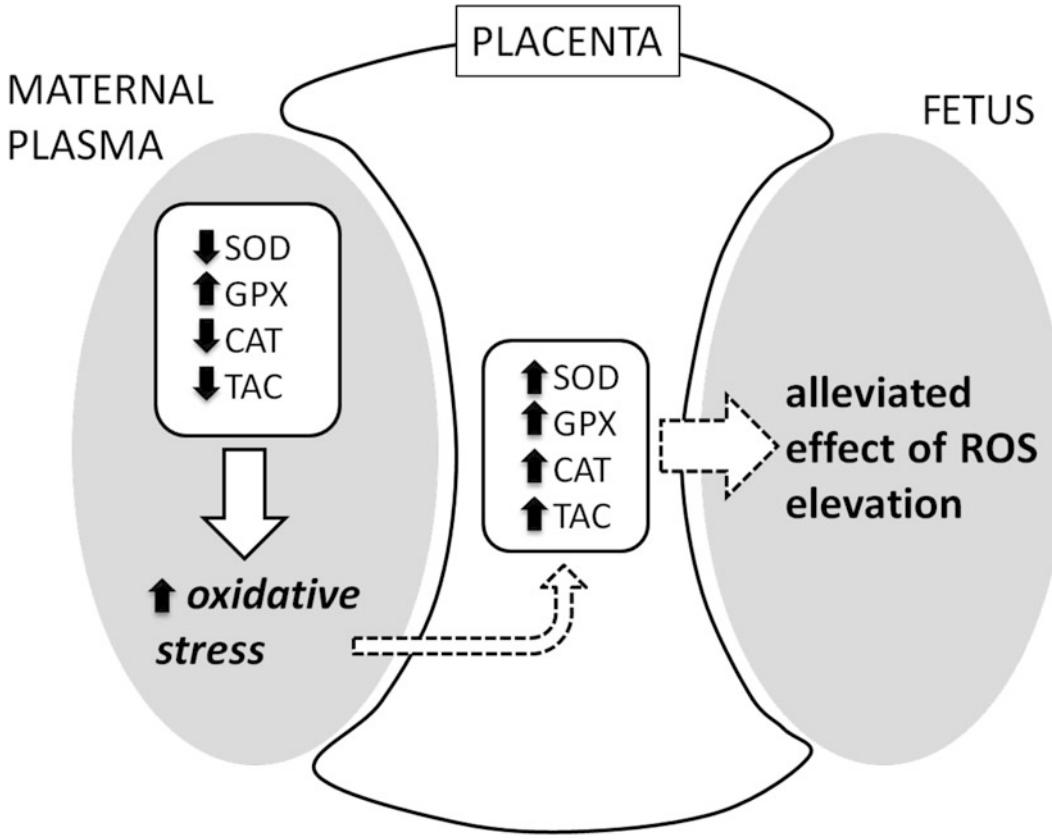


Fig. 26.1 Antioxidant enzymes expression profile between plasma and placenta in GDM (Representation of observed changes in antioxidant enzymes expression profile between plasma and placenta in GDM. Elevated systemic oxidative stresses in addition to a low antioxidant protection trigger a maintained oxidative milieu which induced an elevation of antioxidant enzymes expression. This issue does not get to eliminate oxidative stress in placenta but could be related with an alleviation of oxidative environment in fetus. *SOD* superoxide dismutase; *GPX* glutathione peroxidase; *CAT* catalase; *TAC* total antioxidant capacity)

with respect to adiponectin [30], and higher levels of leptin post-partum [31–33]. However, other research groups have found high levels of TNF-α [34] and IL-6 [35], and low adiponectin levels in the post-partum period [31, 32, 36]. Serum TNF-α has been shown to be inversely related to insulin sensitivity, and has been proposed as an independent predictor of insulin sensitivity and GDM [3].

Several AMs are implicated in the pathogenesis of endothelial damage, and act in early stages of atherosclerosis development. We observed that ICAM-1, VCAM-1, and E-selectin levels were slightly higher (albeit not statistically significant) in all cases we studied (Table 26.2), and that ICAM-1 levels were higher in patients with greater deterioration of carbohydrate metabolism, insulin resistance, and MetS in the post-partum period [37]. Significantly higher levels of ICAM-1 and VCAM-1 [38] and also E-Selectin [39] have been described post-delivery in women with previous GDM. Conversely, Retnakaran et al. [40] found that E-selectin and VCAM-1 decreased 12 weeks after delivery in controls and remained unchanged in GDM post-partum. Lawrence et al. observed no differences in E-selectin levels and no correlation with insulin resistance [41]. Similarly, Sokup et al. [42] observed decreased hs-CRP and ICAM-1 after 6 months, and elevated E-selectin after 12 months (after adjustment for age, BMI, waist circumference and 2 h oral glucose tolerance test (OGTT).

Table 26.2 Adipokines, adhesion molecules, and oxidative stress and antioxidant markers in women with previous GDM (cases) and without GDM (controls)

Characteristics	Cases	Controls	p
TNF-α (pg/ml)	4.8 ± 1.7	4.9 ± 1.2	0.789
IL-6 (pg/ml)	2.1 ± 1.2	2.1 ± 1.8	0.859
Leptin (pg/ml)	32,025 ± 19,917	20,258 ± 16,359	0.023
Adiponectin (ng/ml)	15,398 ± 4778	16,892 ± 4383	0.264
Selectin (ng/ml)	98.1 ± 65.7	81.7 ± 54.6	0.349
VCAM (ng/ml)	1414.8 ± 483.1	1281 ± 318.1	0.256
ICAM (ng/ml)	329.1 ± 174.0	263.1 ± 114.9	0.122
LPO (μM)	10.3 ± 3.3	10.5 ± 2.8	0.88
TAC (mM)	3.1 ± 0.4	3.1 ± 0.4	0.90
GPX (μmol/min/mL)	80.0 ± 21.8	83.5 ± 17.5	0.52
Catalase (nmol/min/mL)	38.7 ± 15.6	28.9 ± 11.1	0.013
GSH (μmol/min/mL)	6.9 ± 2.1	5.9 ± 1.6	0.055
GST (μmol/min/mL)	2.7 ± 2.8	2.5 ± 2.7	0.64
SOD (U/mL)	1.8 ± 0.3	1.7 ± 0.4	0.36

Data expressed as means ± SD

TNF-α tumor necrosis factor alpha; *IL-6* interleukin 6; *ICAM-1* intercellular adhesion molecule-1; *VCAM-1* vascular adhesion molecule-1; *E-selectin* cellular molecule; *LPO* lipoperoxides; *GSH* Glutathione reductase; *GST* glutathione transferase; *SOD* superoxide dismutase; *GPX* glutathione peroxidase; *TAC* total antioxidant capacity

Post-partum Oxidative Stress Markers in Women with Previous GDM

Oxidative stress may be implicated in GDM progression and/or pathogenesis with reduced antioxidants defenses reflecting a poor protective response against oxidative stress [13]. In an earlier study [37], differences in oxidative stress markers were significantly higher in cases compared to controls at post-partum with respect to catalase levels, and the differences were approaching statistical significance with respect to GSH levels (Table 26.2). In addition, catalase showed a significant positive correlation with glucose intolerance. There were no significant differences when we evaluated the influence of obesity on oxidative stress parameters. In multivariate analysis, higher GSH and catalase levels were significantly associated with the history of GDM. We found no publications on GPX in the post-partum period. In a prospective analysis, increases in LPO and decreases in TAC levels in women with T2DM, T1DM, and GDM have been observed [16]. Our post-partum analyses revealed no statistically significant differences either in GSH or LPO levels in our cases [37].

It is still unclear whether a diet rich in antioxidants, or antioxidant supplementation of the diet, could improve oxidative stress in GDM, and prevent the subsequent development of T2DM [43]. Dietary supplementation with a mixed pool of antioxidants can reduce oxidative stress and inflammation in healthy subjects. More importantly, in prediabetic patients, these supplements have an important role in endothelium protection before irreversible endothelial damage has occurred [44]. Numerous epidemiological studies have shown that dietary intake of vitamin E is inversely associated with the risk of CVD, though randomized intervention trials have been equivocal with regard to cardiovascular benefit from vitamin treatment. In general, the epidemiological studies suggest that prevention of CVD requires large amounts of vitamin E, in excess of the conventional dietary intake and, hence, there is considerable uncertainty as to the optimal dose of vitamin E supplementation [45].

Recommendations and Guidelines

Our published data suggest that oxidative stress and inflammation are involved in the pathogenesis of diabetic endothelial dysfunction. New noninvasive technologies can detect tissue damage mediated by advanced glycoxidation endproduct (AGE) formation; these include indirect measures such as pulse wave analysis (a marker of vascular dysfunction) and more direct markers such as skin auto-fluorescence (a marker of long-term accumulation of AGEs). In the future, we can be optimistic that new blood and tissue-based biomarkers will enable the detection, prevention, and treatment of diabetes and its complications long before overt disease develops.

As atherosclerosis is a chronic condition commencing in youth, and because clinical events may be silent in patients with diabetes, surrogate measures of hormonal, metabolic, and vascular changes occurring in such women during pregnancy (and over the post-partum years) are important for early identification of diabetic patients who are at high risk of vascular damage. These markers would, as well, facilitate monitoring the efficacy of interventions. Early predictors of vascular damage are vital for appropriate implementation of intensive treatment strategies and, as a consequence, reduce the potential CVD burden.

We affirm that further studies are needed to evaluate the changes in adipokines, AMs, and oxidative stress. Their potential causal relationships with vascular and metabolic changes need to be evaluated in women with GDM since this condition is, often, a precursor to subsequent adult diseases, in mothers as well children.

Conclusions

The development of gestational diabetes, or even milder forms of dysglycemia during pregnancy, represents an increased risk for developing T2DM, MetS and, over time, overt CVD.

Our studies have shown that women with previous GDM have a higher prevalence of MetS, significant differences in blood pressure, uric acid levels, as well as carbohydrate, lipid, adipokine, oxidative stress, and endothelial function profiles; all of which being important factors for future development of CVD.

Elevated levels of circulating markers of endothelial dysfunction in young females with GDM history could reflect an early stage along the pathway to the future development of cardio-metabolic disorders. There is a paucity of evidence in the published literature regarding AM levels either in relation to vascular and metabolic changes in women with previous GDM or in relation to their possible involvement in future T2DM development.

Acknowledgements The details reported in this manuscript are derived from studies that have been supported by grants from *Consejería de Salud, Junta de Andalucía* (grants: PI-405/06; PI-0525-2012). Editorial assistance was by Dr. Peter R Turner.

Disclosure The authors declare that there are no conflicts of interest in the conduct of the studies reported in this manuscript.

References

1. Montonen J, Knekt P, Järvinen R, et al. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care. 2004;27:362–6.
2. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and β-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. Eur J Clin Invest. 2002;32:24–34.

3. Kirwan JP, Hauguel-De Mouzon S, Lepercq J, et al. TNF-α is a predictor of insulin resistance in human pregnancy. Diabetes. 2002;51:2207–13.
4. Winkler G, Cseh K, Baranyi E, et al. Tumor necrosis factor system in insulin resistance in gestational diabetes. Diabetes Res Clin Pract. 2002;56:93–9.
5. Lopez-Tinoco C, Roca M, Fernandez-Deudero A, et al. Cytokine profile, metabolic syndrome and cardiovascular disease risk in women with late-onset gestational diabetes mellitus. Cytokine. 2012;58:14–9.
6. Gao X, Yang H, Zhao Y. Variations of tumor necrosis factor- α, leptin and adiponectin in mid-trimester of gestational diabetes mellitus. Chin Med J. 2008;121:701–5.
7. Horosz E, Bomba-Opon DA, Szymanska O, et al. Third trimester plasma adiponectin and leptin in gestational diabetes and normal pregnancies. Diabetes Res Clin Pract. 2011;93:350–6.
8. Xu J, Zhao YH, Chen YP, et al. Maternal circulating concentrations of tumor necrosis factor-alpha, leptin, and adiponectin in gestational diabetes mellitus: a systematic review and meta-analysis. Sci World J. 2014;2014:1–12.
9. Krauss T, Emons G, Kuhn W, et al. Predictive value of routine circulating soluble endothelial cell adhesion molecule measurements during pregnancy. Clin Chem. 2002;48:1418–25.
10. Kautzky-Willer A, Fasching P, Jilma B, et al. Persistent elevation and metabolic dependence of circulating E-selectin after delivery in women with gestational diabetes mellitus. J Clin Endocrinol Metab. 1997;82:4117–21.
11. Mordwinkin M, Ouzounian JG, Yedigarova L, et al. Alteration of endothelial function markers in women with gestational diabetes and their fetuses. J Matern Fetal Neonatal Med. 2013;2:507–12.
12. Jenkins AJ, Best JD, Klein RL, et al. Lipoproteins, glycoxidation and diabeticangiopathy. Diabetes Metab Res Rev. 2004;20:349–68.
13. Peuchant E, Brun JL, Rigalleau V, et al. Oxidative and antioxidative status in pregnant women with either gestational or type 1 diabetes. Clin Biochem. 2004;37:293–8.
14. Rajdl D, Racek J, Steinerova A, et al. Markers of oxidative stress in diabetic mothers and their infants during delivery. Physiol Res. 2005;54:429–36.
15. Orhan H, Önderoglu L, Yücel A, et al. Circulating biomarkers of oxidative stress incomplicated pregnancies. Arch Gynecol Obstet. 2003;267:189–95.
16. Toescu V, Nuttall SL, Martin U. Changes in plasma lipids and markers of oxidative stress in normal pregnancy and pregnancies complicated by diabetes. Clin Sci. 2004;106:93–8.
17. Karacay O, Sepici-Dincel A, Karcaaltincaba D, et al. A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24–36 weeks of gestation. Diabetes Res Clin Pract. 2010;89:231–8.
18. Zhu C, Yang H, Geng Q, et al. Association of oxidative stress biomarkers with gestational diabetes mellitus in pregnant women: a case-control study. PLoS ONE. 2015;10:e0126490.
19. Lopez-Tinoco C, Roca M, Garcia-Valero A, et al. Oxidative stress and antioxidant status in patients with late-onset gestational diabetes mellitus. Acta Diabetol. 2013;50:201–8.
20. Madazli R, Tuten A, Calay Z, et al. The incidence of placental abnormalities, maternal and cord plasma malondialdehyde and vascular endothelial growth factor levels in women with gestational diabetes mellitus and nondiabetic controls. Gynecol Obstet Invest. 2008;65:227–32.
21. Chen X, Scholl TO. Oxidative stress: changes in pregnancy and with gestationaldiabetes mellitus. Curr Diab Rep. 2005;5:282–8.
22. Surapaneni KM, Vishnu Priya V. Antioxidant enzymes and vitamins in gestational diabetes. J Clin Diagn Res. 2008;2:1081–85.
23. Kinalski M, Sledziewski A, Telejko B, et al. Lipid peroxidation, antioxidant defence and acid-base status in cord blood at birth: the influence of diabetes. Horm Metab Res. 2001;33:227–31.
24. López Tinoco C, Segundo C, Aguilar Diosdado M. Gestational diabetes and oxidative stress. Curr Trends Endocrinol. 2014;7:45–55. ISSN: 0972-947X.
25. Roca-Rodríguez MM, López-Tinoco C, Fernández-Deudero A, et al. Diabetes adipokines and metabolic syndrome risk-factors in women with previous gestational diabetes mellitus. Metab Res Rev. 2012;28:542–8.
26. Di Cianni G, Lencioni C, Volpe L, et al. C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab Res Rev. 2007;23:135–40.
27. Xu Y, Shen S, Sun L, et al. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS ONE. 2014;9:e87863.
28. Sokup A, Góralczyk B, Góralczyk K, et al. Triglycerides as an early pathophysiological marker of endothelial dysfunction in nondiabetic women with a previous history of gestational diabetes. Acta Obstet Gynecol Scand. 2012;91:182–8.
29. Di Cianni G, Lencioni C, Volpe L, et al. C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab Res Rev. 2007;23:135–40.
30. Saucedo R, Zarate A, Basurto L, et al. Relationship between circulating adipokines and insulin resistance during pregnancy and postpartum in women with gestational diabetes. Arch Med Res. 2011;42:318–23.

31. Boyadzhieva M, Atanasova I, Zacharieva S, et al. Adipocytokines during pregnancy and postpartum in women with gestational diabetes and healthy controls. J Endocrinol Invest. 2013;36:944–9.
32. Liu T, Fang Z, Yang D, et al. Correlation between the inflammatory factors and adipocytokines with gestational diabetes mellitus and their change in puerperium. Zhonghua Fu Chan Ke Za Zhi. 2012;47:436–9.
33. McLachlan KA, O'Neal D, Jenkins A, et al. Do adiponectin, TNFα, leptin and CRP relate to insulin resistance in pregnancy? Studies in women with and without gestational diabetes, during and after pregnancy. Diabetes Metab Res Rev. 2006;22:131–8.
34. Friedman JE, Kirwan JP, Jing M, et al. Increased skeletal muscle tumor necrosis factor-alpha and impaired insulin signaling persist in obese women with gestational diabetes mellitus 1 year postpartum. Diabetes. 2008;57:606–13.
35. Morisset AS, Dubé MC, Côté JA, et al. Circulating interleukin-6 concentrations during and after gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2011;90:524–30.
36. Vitoratos N, Valsamakis G, Mastorakos G, et al. Pre- and early post-partum adiponectin and interleukin-1beta levels in women with and without gestational diabetes. Hormones (Athens). 2008;7:230–6.
37. Roca-Rodríguez MM, López-Tinoco C, Murri M, et al. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus. J Endocrinol Invest. 2014;37:503–9.
38. Göbl CS, Bozkurt L, Prikoszovich T, et al. Estimating the risk after gestational diabetes mellitus: can we improve the information from the postpartum OGTT? Am J Physiol Endocrinol Metab. 2013;304:E524–30.
39. Sokup A, Ruszkowska B, Góralczyk B, et al. Elevation of sE-selectin levels 2–24 months following gestational diabetes is associated with early cardiometabolic risk in nondiabetic women. Int J Endocrinol. 2012;2012:278050.
40. Retnakaran R, Qi Y, Connelly PW, et al. Risk of early progression to prediabetes or diabetes in women with recent gestational dysglycaemia but normal glucose tolerance at 3-month postpartum. Clin Endocrinol (Oxf). 2010;73:476–83.
41. Lawrence NJ, Kousta E, Penny A, et al. Elevation of soluble E-selectin levels following gestational diabetes is restricted to women with persistent abnormalities of glucose regulation. Clin Endocrinol (Oxf). 2002;56:335–40.
42. Sokup A, Ruszkowska-Ciastek B, Walentowicz-Sadłecka M. Heterogeneity of cardiovascular risk factors profile in non-diabetic women 2–24 months post gestational diabetes mellitus. Gynecol Endocrinol. 2014;30:350–4.
43. Montonen J, Knekt P, Jarvinen R, et al. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care. 2004;27:362–6.
44. Di Pino A, Maiorca D, Judica A, et al. Effects of antioxidants on postprandial oxidative stress and endothelial dysfunction in subjects with impaired glucose tolerance and type 2 diabetes. Eur J Nutr. 2010;49:409–16.
45. Mezzetti A, Cipollone F, Cuccurullo F. Oxidative stress and cardiovascular complications in diabetes: isoprostanes as new markers on an old paradigm. Cardiovasc Res. 2000;47:475–88.

Chapter 27
Neurodevelopmental Outcome in Offspring Born Following Gestational Diabetes

Malcolm Battin, Trecia A. Wouldes and Janet Rowan

Key Points

- The literature on neurodevelopmental follow-up following GDM is often limited by small numbers or inadequate information on diabetes type or control of maternal DM.
- There is a complex interplay of social factors, obesity and environment that needs to be fully accounted for when assessing neurodevelopmental and cognitive outcomes following GDM.
- The studies describing school age follow-up demonstrate a concerning pattern of lower cognitive scores, attention issues, hyperactivity and poor fine motor skills following maternal GDM.
- The studies using data linkage analysis reinforce concerns regarding neurodevelopmental outcome following maternal GDM and raise the issue of ASD.
- Based on the follow-up of two studies reporting no differences between treatment groups, there were no concerning effects from treatment with metformin versus insulin.
- Future work is required with a need for school age outcome data on contemporary cohorts of offspring following GDM that has been pharmacologically treated.
- There must continue to be efforts to reverse or slow down the epidemic of obesity and the related intergenerational effects of conditions such as GDM.

Keywords Neurodevelopmental outcome · Developmental delay · Autistic spectrum abnormality · Hyperactivity · Metformin · Insulin

Abbreviations

GDM	Gestational Diabetes Mellitus
DM	Diabetes Mellitus
BSID-II	Bayley Scales of Infant Development, Version 2
MDI	Mental Development Index
PDI	Psychomotor Development Index

M. Battin (✉)
Newborn Services, Auckland City Hospital & Department of Paediatrics, University of Auckland, Park Road, Auckland, New Zealand
e-mail: malcolmb@adhb.govt.nz

T.A. Wouldes
Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand
e-mail: t.wouldes@auckland.ac.nz

J. Rowan
National Women's Health, Auckland City Hospital, 2 Park Road, Auckland, New Zealand
e-mail: JRowan@adhb.govt.nz

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_27

NEPSY	Developmental Neuropsychological Assessment
ASD	Autistic Spectrum Disorder
GCSE	General Certificate of Secondary Education
IQ	Intelligence Quotient
ADHD	Attention Deficit Hyperactivity Disorder
MiG trial	Metformin in Gestational diabetes

Introduction

There are three main reasons why reviewing the published literature regarding neurodevelopmental outcomes of offspring following pregnancies complicated by Gestational Diabetes Mellitus (GDM) might be important and timely. The primary reason is that society is facing an epidemic of obesity and as a consequence associated conditions, such as GDM, are becoming more common. Indeed, GDM rates are reported to be increasing worldwide with estimates of prevalence rates rising to as high as 18–36%. [1, 2]. Given this increase in rate and the important role of antenatal events in determining long-term childhood and adult outcomes [3, 4], even a small increase in any adverse effect on offspring associated with maternal GDM would have important population health implications. The focus of this chapter will be neurodevelopmental outcomes of offspring of mothers with GDM. However, there is also substantial evidence linking foetal metabolic status, body composition and long-term cardiovascular health [3–6]. The second reason for this review is that there is a need to determine the safety and efficacy of pharmacological interventions for GDM; subsequent neurodevelopment of the offspring is an essential component of that safety profile. The third reason is to identify significant gaps in published research, which limits the evidence base for writing GDM guidelines that aim to improve care for women and their offspring. Examples of this could be an incomplete understanding of effect size or mechanisms of harm causation or problems in differentiation between the effects of GDM and those associated with social circumstance, obesity and/or treatment. Thus a good understanding of the literature will help to set the research agenda.

Metabolic Disturbance in GDM

The effect of the maternal metabolic environment in GDM upon the foetus is well recognised and has been previously well summarised in reviews by Kjos [7] and Reece [8], and will also be covered in other chapters in this book. The fundamental issue is that maternal hyperglycaemia results in an excessive glucose supply to the foetus, which causes an upregulated foetal insulin response [9]. In utero insulin acts as a growth hormone [10] so elevated levels are associated with an increase in foetal size. In addition, there are likely to be many other factors that could influence foetal growth including placental function, epigenetic modification plus elevated concentrations of other nutrients, such as amino acids and lipids [11].

The neurodevelopmental effects of the metabolic disturbance on the developing foetus are likely to vary depending on gestation and duration of exposure. At critical developmental stages early in pregnancy high glucose levels can act as a teratogen causing problems in embryogenesis and resulting in major congenital anomalies affecting the cardiovascular, musculoskeletal, neurological and genito-renal systems [12]. However, in GDM the onset of maternal metabolic disturbance is characteristically in the second half of pregnancy from around the 20th week. Although the organs are

formed at this point, the foetus is immature and prone to adverse effects from metabolic disturbance. Two commonly noted issues that occur due to foetal hyperinsulinaemia are neonatal hypoglycaemia and foetal/neonatal macrosomia. There is also a theoretical risk of hypoglycaemia associated with maternal pharmacological treatment of GDM. Neonatal hypoglycaemia may be associated with neurological injury [13, 14], particularly if the episode is prolonged and/or severe. In addition, macrosomia may be associated with significant complications of labour and delivery [7] and there is potential for adverse effects on neurodevelopment via sentinel events and secondary asphyxial injury. Although the metabolic disturbance from GDM has a later onset than that from type 2 or type 1 diabetes mellitus (DM), it is still associated with a high rate of neonatal unit admission [15] and other neonatal disorders including jaundice, respiratory distress syndrome and polycythemia [7].

With respect to possible neurodevelopmental issues, it should be noted that, the foetal central neurological system still has to undergo considerable maturation after the typical onset of hyperglycaemia from GDM. The major steps in brain development are summarised in Table 27.1. Between approximately three and five months gestation, there is neuronal migration. This is followed by ongoing organisation of brain structure including Subplate neurone differentiation, lamination, synaptogenesis plus glial proliferation and differentiation. Myelination starts in the third trimester and continues into childhood. The immature brain is vulnerable to several putative mechanisms of injury. Hyperglycaemia is linked with an increase in metabolic activity [16] and an associated increase in oxygen consumption [17]. Furthermore, the offspring from pregnancies affected by diabetes may develop polycythemia and elevated erythropoietin, which has been associated with low levels of iron in the brain and other organs [18]. Iron has a role in several stages of neurological development and deficiency may negatively affect cortical development. Thus, asphyxia and relative iron deficiency may be a potential mechanism for impairment of neurodevelopment, in addition to any direct effects from hyperglycaemia. Although the immature brain is generally vulnerable to insult, it is notable that the immature hippocampus is especially prone to damage from hypoglycaemia [19] and hypoxia [20, 21].

There may be other pathways whereby development is affected by the effects of GDM or pre-existing maternal diabetes. One animal study performed in rats [22], reported that maternal hyperglycemia can retard dendritic development in the foetal brain perhaps as a result of abnormal insulin/IGF-I signalling. Other studies have reported lower levels of docosahexaenoic acid in the offspring of diabetic mothers and linked this to early childhood development at 6 months [23]. The severity of metabolic disturbance is important as it is linked with both complications and outcomes. In an older study of mothers with diabetes [24], birth weight, as an indirect marker of maternal glucose level, was negatively correlated to intellectual status at both 3 and 5 years of age.

From the onset, it should be recognised that there are some challenges in reviewing the published literature on neurodevelopmental outcomes of offspring born following pregnancy complicated by GDM. An important primary issue is confirming that the study group reported is correctly attributed as exposed to GDM rather than pre-existing diabetes. Although GDM is the most common form of diabetes affecting pregnant women, for the purposes of reviewing neurodevelopment, it would clearly be inappropriate to include babies with foetal anomalies associated with early pregnancy hyperglycaemia from type 1 or type 2 DM. So ideally the publication reporting neurodevelopment would

Table 27.1 Summary of major steps in human brain development

Stage of development	Timing
Primary neuralation	3–4 weeks gestation
Prosencephalic dev.	2–3 months gestation
Neuronal proliferation	3–4 months gestation
Neuronal migration	3–5 months gestation
Organisation	5 months–years
Myelination	Up to years postnatal

include details of how the GDM diagnosis was made, which is less consistent in the older literature. Although studies are usually clear about type 1 DM, problems could arise if a GDM cohort includes cases with hyperglycaemia first detected in pregnancy and any investigation performed to exclude type 2 DM was not described. In addition, even when the diagnosis of GDM has been ascribed to the correct number of children within a cohort, there still may be a small sample size for children exposed or a paucity of information on maternal glucose control during pregnancy. Notwithstanding this requirement to establish a clear diagnosis of GDM, there will be some overlap in pathways leading to neurological insult such as postnatal hypoglycaemia or sentinel events associated with macrosomia so some studies with a poorly differentiated maternal diabetes status may be included in this review.

Studies Reporting Neurodevelopmental Outcomes for Offspring Born After GDM

Two main types of study methodologies may be used to determine the effect, if any, of GDM on neurodevelopmental outcomes:

1. Establish cohorts of children who have been identified as exposed in utero to GDM then follow-up to study outcome
2. Use large pre-existing datasets and link pregnancy data including GDM status with subsequent routinely collected neurodevelopmental information

There are advantages and disadvantages to either method. Using a cohort study it may be easier to ensure that each case fits pre-specified inclusion criteria. However, the follow-up has to be for sufficient time without excessive dropout and the cohort must be of sufficient size to have power to detect an effect, if present. Linkage studies utilise large datasets that have more statistical power, but these datasets are pre-existing and may have been collected for an entirely different purpose. Therefore, they may not contain exactly the information desired such as details on the type of diabetes affecting the mother in pregnancy and the level of glucose control. Either approach may necessitate controlling for other possible factors such as socioeconomic status and environmental factors.

Studies Reporting Preschool Neurodevelopmental Outcomes

There are very few published cohorts reporting outcome in early preschool children born following maternal GDM. Moreover, the numbers in each cohort are sometimes small and data were often collected as part of studies that also include maternal type 1 and type 2 DM. Finally, the reports do not include any evidence of blinding of follow-up assessments to maternal diabetes status.

In a series of early reports, Rizzo [25] studied the offspring of 223 women from Chicago with a singleton pregnancy. Ninety nine women had GDM, a further 89 women had pre-gestational diabetes and 35 had no impairment of maternal glucose metabolism. Assessment was with the Bayley Scales of Infant Development, Version 2 (BSID-II) at age two years. There were no differences in corrected mean Mental Development Index (MDI), which was 90 for the GDM group and 89 in both the pre-gestational DM and non-diabetic groups. This finding remained after correction for important factors including socioeconomic status, ethnicity and antepartum glucose control. Further, there were no significant correlations between neurodevelopment and the occurrence of perinatal complications. The authors concluded that there were minimal effects of perinatal complications on the neurodevelopment of offspring following maternal diabetes.

Table 27.2 Summary of studies reporting a significant difference in preschool BSID-II by GDM status

Study	Group	BSID (II) MDI	BSID (II) PDI
Zornoza-Moreno [28] at 6 months of age	Control n = 23	103	92
	GDM (diet) n = 21	100	82
	GDM (Insulin) n = 19	94	82
DeBoer [26] at 12 months	GDM n = 14	95	89
	No GDM n = 29	103	102
Rizzo [25] at 2 years	GDM n = 99	90	–
	Pre-gestational DM n = 89	89	–
	Non-diabetic group n = 35	89	–

Two small studies examining other aspects of GDM outcome have reported limited neurodevelopmental information. The first study from Minnesota, focussed on explicit memory performance at 12 months, in the offspring of diabetic women with uncomplicated pregnancies [26] but also reported mean BSID-II MDI and PDI scores that were lower in the offspring of diabetic women compared with controls (MDI 95 vs. 103 and PDI 89 vs. 102). Adjustment was made for gestational age differences but the population studied was very selective and it is stated that the sample consisted of "predominantly (91%) Caucasian infants born to families of middle to high income". Furthermore, numbers were very small with follow-up of only 13 infants of diabetic women and it was not clear whether the women had pre-gestational diabetes or GDM, or how their diabetes was managed. The second study from New York [27] explored the interaction between GDM and socioeconomic status. Neuropsychological outcomes were measured with the Developmental Neuropsychological (NEPSY) assessment at 3–4 years and WPPSI-II in four groups designated by the presence of one, both or neither GDM or low socioeconomic status. Although there were differences between the groups and infants exposed to both GDM and low socioeconomic status performed worst, there were only 12 infants with the single risk of being exposed to GDM. There was an increase in ADHD in later childhood and lower NEPSY scores when GDM was accompanied by low socioeconomic status but the effect in the preschool epoch based on GDM alone was less discernible. So, from these two studies, it is hard to make any firm conclusions regarding neurodevelopment associated solely with GDM.

In a more recent prospective study from Spain, Zornoza-Moreno et al. [28] assessed neurodevelopment using BSID-II at 6 and 12 months of age in the offspring of 63 pregnant women including 23 controls, 21 diet-controlled GDM and 19 insulin-treated GDM. At 6 months the GDM infants had lower mean scores than the controls. In addition there was a gradient reflecting GDM severity as evidenced by treatment with insulin (Table 27.2). This difference was still present after adjusting for confounding factors including breastfeeding, maternal education and gender. At 12 months there was still a trend towards lower scores but this was no longer statistically significant.

Studies Reporting School Age Neurodevelopmental Outcomes

Although there are a few more studies on neurodevelopment at school age, the numbers of participants in most of the studies are still modest and assessment is by a variety of measures so the literature needs careful scrutiny. One of the early cohort studies reporting neurodevelopmental outcomes was from Sweden, in which Persson [29] reported the outcome of 94 infants born between 1969 and 1972 following pregnancy complicated by diabetes. Of the children followed up at five years of age all were reported to have normal physical and neurological development. However, most cases were type 1 DM and only 20 infants who were assessed at five years were born after GDM.

Furthermore there was a significant loss to follow-up and those infants who were not followed had more perinatal complications and congenital malformations than those followed. These issues mean it is not possible to reliably detect any effect of GDM.

Rizzo performed further follow-up of the group previously described at preschool age [25], which included the offspring of 99 women with GDM, 89 women with pre-existing diabetes and 35 with no impairment of maternal glucose metabolism. Neurodevelopmental outcomes were obtained using the Stanford–Binet Intelligence Scale up to 5 years. There were no significant differences in corrected mean Stanford–Binet with scores of 93, 89 and 92 for GDM, pre-gestational diabetes group and non-diabetic groups respectively [25]. After correction for socioeconomic status, ethnicity and antepartum glucose control, there were no significant correlations between childhood IQ and perinatal complications. The author concluded that the effects of perinatal complications on the intellectual development of offspring of diabetic mothers appeared minimal. However, in another report by this group [30], BSID-II scores and motor proficiency scores at 6–9 years were correlated with maternal metabolic control. The author's overall conclusion from this body of work was that metabolic control influences the neurodevelopmental outcome but that most perinatal complications and long-term adverse outcomes can be mitigated by management of the diabetes plus obstetric and neonatal care.

In contrast, two other studies report an increased rate of neurodevelopmental concerns in school age offspring born following GDM. In the first study from Israel [31], a series of neuropsychological tests were performed in 32 school age children born following well-controlled GDM and compared with those from 57 age matched control children. At 9 years the children in the GDM group had a higher rate of attention deficit, lower cognitive scores and performed less well on testing of fine and gross motor function. There was no correlation between performance and severity of perinatal complications and the differences tended to be less overt with age. The study authors concluded that the presence of metabolic abnormality associated with GDM in the second half of pregnancy produced minor neurological deficits that were more pronounced in younger children. The same group [32] investigated offspring born following GDM and those born following pre-existing diabetes and reported that the children from both groups had more inattention and hyperactivity as detected by the Pollack Taper test. Their scores were also non significantly higher on the Conner's Abbreviated Parents-Teachers Questionnaire, which evaluates hyperactivity and inattention. The second study from Mexico by Bolanos [33], described the follow-up of 32 children, aged 7–9 years, born to mothers with GDM and compared performance on cognitive tasks with that in 28 children, aged 8–10 years, whose mothers had normal glucose levels in pregnancy. The GDM group had lower performance on graphic, spatial and bimanual skills and more soft neurologic signs than the controls plus lower scores for general intellect and working memory.

Finally, one study from India [34] reported offspring born following GDM to have higher function than controls. In this study, 515 children (32 GDM vs. 483 non GDM) born between 1997 and 1998 were followed as part a birth cohort and were tested at nine years using components of the Kaufman Assessment Battery for Children and additional tests of learning, long-term storage/retrieval, short-term memory, reasoning, attention and concentration, and visuospatial and verbal abilities. The children in the GDM group scored higher on testing of learning, long-term retrieval/storage, reasoning, verbal ability and attention. However, after controlling important variables such as: age, sex, gestation, birth weight and head circumference, maternal age, parity, BMI, socioeconomic status, education and rural/urban residence there was only a significant difference in learning and long-term retrieval/storage and verbal ability. This is the only study that reports better outcome for children born following GDM and it is possible that this reflects a different relationship between socioeconomic status and GDM in an Indian context compared with that in more developed countries. Hence, caution should be used in interpretation of these results to exclude any adverse effect of GDM on the developing nervous system.

Studies Reporting Adult Neurodevelopmental Outcomes

Clausen et al. [35] assessed cognitive function in Danish adults aged 18–27 using a global cognitive score from Raven's Progressive Matrices and three verbal subtests from the Weschler Adult Intelligence Scale. The cohort included 153 offspring from women with diet-treated GDM and 118 controls. A lower global cognitive score was reported for the offspring of women with GDM (93 vs. 100) but the difference was no longer statistically significant after adjustment for important clinical, demographic and social factors such as maternal age, parity, smoking status, maternal/parental education, gender, birth weight, gestational age, perinatal complications and offspring age at follow-up. Similarly, the global cognitive score was lower with increasing maternal fasting and 2 h glucose levels but this relationship was also not significant after adjustment for social class and parental educational level.

The results of these published studies describe the neurodevelopmental outcomes at various ages from preschool through to adulthood for offspring following GDM. The preschool studies potentially suggest an adverse effect on early neurodevelopment associated with maternal GDM but the results are mixed and the ability to detect any difference was limited by the small numbers of GDM involved in some studies. Indeed, there were probably less than 150 offspring born following GDM who underwent assessment between 6 months and 2 years. Also testing at this age was by either BSID-II or NEPSY and specific testing of fine motor skills, memory and attention would not be simple to perform at such an early age when development is dominated by progress in gross motor skills. In two studies performed at school age [32, 33], an increased rate of abnormal assessment was reported after testing memory plus fine motor, spatial and bimanual skills. In addition, hyperactivity, inattention and soft neurological signs were reported. As with the preschool studies the numbers of children tested were again limited. Only a few studies were longitudinal, therefore it is not possible to make a firm comment on the observation from the Ornoy paper that abnormalities tended be more pronounced in younger children. Only one study reported adult outcomes and the results were reassuring with respect to cognitive function following mild in utero hyperglycaemia exposure associated with maternal GDM. In addition, it was again noted that the differences in raw scores were explained by adjusting for factors that were well-recognised predictors of cognitive function.

Behaviour and Special Senses

In some studies, there have been efforts to investigate other factors such as behaviour or special sense function that could be associated with or partially explain IQ differences. Rizzo et al. [36] evaluated children's behavioural adjustment, in a sample of 201 mothers (68 with pre-gestational diabetes, 50 with gestational diabetes, and 83 with non-diabetic pregnancies) and their singleton offspring. After adjustment for socioeconomic status, ethnicity and maternal attitudes, there was no correlation between the Child Behavior Checklist ratings and maternal patient group. However, childhood obesity correlated positively with internalizing behaviour problems.

Special Senses

A large study by Dionne [37] followed 1835 singleton infants born between 1997 and 1998 plus 998 twins born between 1995 and 1998. The cohort included 221 infants of gestational diabetic mothers (105 singletons and 116 twins) with language tested at 18, 30, 42, 60 and 72–84 months. At 18 and 30 months the infant's scores for expressive vocabulary and expressive grammar were lower than controls. This was reported as equivalent to a 4–12 word difference in vocabulary of 77 words or up

to 10 words in 100. In addition 87% of controls, but only 74% of those born following GDM, were using word combinations by 30 months. Whilst testing at 42 and 60 months did not reveal any differences between the two groups at the 72–84 months follow-up, those born following GDM performed 0.35 SD below controls on an oral communication scale. The author's conclusion was that exposure to GDM was associated with delayed expressive language through to middle childhood.

Of interest is the research linking impaired language with work examining auditory recognition in infants of diabetic women. Although the studies included relatively small numbers of infants and are not restricted to maternal GDM, they are included in order to give insight into potential mechanisms of impairment following maternal GDM. Deregnier [38] studied 32 normal newborn infants and 25 infants of diabetic mothers to evaluate the integrity of neural pathways for auditory recognition memory. This recognition memory was assessed by the event-related potential produced in response to the mother's voice, which were then compared to those produced in response to a stranger's voice. BSID-II were performed at 12 months of age and results correlated with recognition memory findings. The infants born following maternal diabetes in pregnancy had subtle evidence of recognition memory impairment. Although infants from both groups demonstrated recognition of the mother's voice, the pattern was different for the stranger's voice with the control group having a negative slow wave that was attenuated in the infants of diabetic mothers. Building on this study, the same group [39] evaluated tactile to vision recognition memory at 8 months of age by palpation of an object without seeing it then testing visual recognition of the object. Infants of diabetic mothers did not manifest any evidence of recognising the palpated object, and although both groups had BSID-II scores in the normal range, the authors concluded that there was evidence of subtle impairment in hippocampal recognition memory.

Epidemiological Studies

An alternative approach to identifying potential neurodevelopmental effects of GDM is to use data linkage in large epidemiological studies. Several studies using such methodology have been published.

An early linkage study [40] used the Swedish Medical Birth Register and the Swedish School Mark Register, which contains school marks for Swedish children on leaving school. For the years 1973–1986 there were 6397 children identified whose mothers had diabetes diagnosed during pregnancy. However, it was not possible to differentiate the type of diabetes. The marks for infants born after DM were lower than those from control children with no diagnosis of diabetes with the effect persisting after adjustment for important perinatal and social confounders. Although the authors concluded that children of mothers with diabetes during pregnancy performed less well than reference children at compulsory school leaving, the cohort was likely to contain significant numbers of Type 1 diabetes and it is not possible to extrapolate any effect purely due to GDM.

Xiang et al. [41] used a large retrospective multi-ethnic longitudinal cohort of 322, 323 singleton children born in 1995–2009 at Kaiser Permanente Southern California hospitals to estimate the relative risk for birth year of autistic spectrum disorder (ASD) associated with intrauterine exposure to pre-existing type 2 diabetes and GDM. In total 3388 children had been diagnosed with ASD of these 130 had been exposed to GDM prior to 26 weeks and 180 had been exposed to GDM after 26 weeks gestation. Analysis, using a model that adjusted for important confounding factors, revealed GDM diagnosed at 26 weeks or earlier to be associated with an increased risk of ASD equal to a hazard ratio of 1.42. Further analysis excluded antidiabetic medication as an independent risk factor for ASD and adjustment for family history of ASD in mother or older sibling did not alter the risk.

Fraser et al. [42] used the data set from the Avon Longitudinal Study of Parents and Children, a large UK prospective pregnancy cohort, and linked with data from school entry and WISC-III IQ at

age 8 plus General Certificate of Secondary Education (GCSE) results at age 16. In this large data set an adverse effect on offspring school age entry scores, IQ at age 8, and GCSE results was demonstrated for both maternal pre-existing diabetes and GDM. A similar but smaller effect was reported for maternal glycosuria. The analysis included adjustment for important factors including: sex, maternal age, pre-pregnancy BMI, smoking in pregnancy, parity, caesarean section, maternal education, and occupational social class. Specifically with regard to offspring following GDM there was an average of five point lower IQ compared to offspring born uncomplicated by maternal diabetes or glycosuria.

In a further study, Fraser et al. [43] investigated the association between maternal diabetes in pregnancy and offspring cognitive ability including making an assessment of influence from intrauterine mechanisms or shared familial characteristics. By linking national registers, the investigators established a large prospective cohort study of over 700,000 singleton Swedish-born men and explored the association between maternal diabetes status in pregnancy and educational achievement on completion of compulsory education at 16 plus intelligence quotient (IQ) at the mandatory conscription examination at 18 years of age. GDM was associated with lower offspring cognitive ability after correction for important factors such as year of birth, parity and education with IQ an average of 1.36 points lower. However, this effect was not seen within sibling pairs so the authors concluded that the association between maternal diabetes in pregnancy and offspring cognitive outcomes was likely explained by shared familial characteristics and not by an intrauterine mechanism.

There are several familial and social characteristics that could play a role in determining outcome of offspring following GDM and some of these are examined in the published literature. In the previously mentioned study by Nomura et al. [27] the effect of low socioeconomic status and/or GDM in combination was examined with regard to neurodevelopment and attention deficit hyperactivity disorder (ADHD). In a cohort of 212 preschool children exposed to GDM in utero, they examined the association between a diagnosis of ADHD and low socioeconomic status. In children exposed to both maternal GDM and raised in a family with low socioeconomic status there was a notable increase in risk for ADHD to over 14-fold. The association between maternal nutritional status and psychomotor development has been examined in 355 low-income African-American children [44]. Development was assessed at a mean age of 5.3 years and correlated with maternal pre-pregnancy body mass index and weight gain during pregnancy. Using multiple regression, adjusting for other important factors, the maternal pre-pregnancy BMI was a significant negative predictor of IQ and nonverbal ability. In a separate study, the effect of maternal metabolic status on the neurodevelopment of the offspring, particularly obesity without GDM, has been recently further assessed by following 331 mother and child pairs from Granada, Spain [45]. Based on their pre-gestational body mass index and GDM status the mothers were divided into four groups: overweight (n = 56), obese (n = 64), gestational diabetic (n = 79), and healthy normal weight controls (n = 132). Development was assessed at 6 months and 18 months using Bayley III scales of neurodevelopment. The results of testing at 6 months were counter intuitive with higher scores in the obese group compared to the normal weight group. These effects on language remained significant after adjusting for confounders. However, at 18-month follow-up the previous differences in language and cognition were replaced by a suggestive trend of lower gross motor scores in the overweight, obese, and diabetic groups.

The Effect of Pharmacological Treatment for GDM on Neurodevelopmental Outcomes

With the increasing number of women affected by GDM and the concerns regarding long-term metabolic programming there has been a focus on treatment of GDM, which has been shown to improve pregnancy outcomes [46, 47]. For some women management with diet and lifestyle will be

sufficient but medication maybe required to achieve glucose control for a reasonable number of women. Although insulin was the mainstay of therapy for many years, metformin now has an established role. The original metformin in Gestational diabetes [48] (MiG trial) demonstrated the safety and efficacy of metformin use in GDM with respect to pregnancy outcomes. Neurodevelopment is clearly an important longer term outcome that requires investigation. Metformin crosses the placenta and so exposes the foetus directly to the drug but also via control of glucose levels and any effects of hypoglycaemia. Initial safety data came from one study reporting no adverse effects on the neurodevelopmental outcome [49] in 126 children who were conceived on metformin plus the mother continued to receive treatment with metformin during pregnancy. Follow-up including growth and neurodevelopment was until 18 months and comparison was made with offspring of women who had no history of polycystic ovary syndrome. Motor and social development was measured at 3, 6, 9, and 18 months using a standard questionnaire and no infants were reported to have either motor or social delay.

Although there are a number of studies reporting perinatal outcomes in trials comparing metformin and insulin, there are currently only two trials published that report on neurodevelopmental outcomes. The first of these was published in 2015, Ijäs [50] investigated neurodevelopment in children born to mothers with GDM who were randomised to pharmacological treatment with metformin or insulin. It used data from a structured questionnaire completed at routine child welfare clinics assessing motor, social and linguistic development at the ages of 6, 12 and 18 months. The mothers had been randomised to metformin treatment in 47 cases and insulin in 50. The motor, social or linguistic development evaluated at the age of 18 months did not differ between the groups. The authors concluded that over the short term, metformin did not seem to be harmful with regards to early motor, linguistic or social development. The other study to report outcome [51] is based on follow-up of the original MiG trial. In this study the offspring from 211 women enrolled from two sites: Auckland, New Zealand (128 children) and Adelaide, Australia (83 children) were followed up. Neurodevelopmental assessment using BSID-II was performed between 24 and 36 months. Overall and separately in both centres the cognitive (MDI) and motor (PDI) scores in the metformin group were comparable with those in the Insulin group. Also there were no differences reported between treatment groups in proportions of children with serious health outcomes on follow-up. These findings were very reassuring with regard to the primary outcome of neurodevelopment by treatment group. Despite any concern around metformin readily crossing the placenta, exposing the foetus, there was no evidence from this study that there was any no adverse effect on neurodevelopment. However, the study reports significant and noteworthy differences in scores between sites with a MDI for the NZ and Australian centres respectively. Thus, the mean score for the NZ cohort in both groups was equivalent to approximately 1.0 SD below the standardised mean on both the MDI and PDI (Table 27.3).

As with much of the previously reviewed literature, it was considered that the effect of social and clinical factors played an important role in neurodevelopmental outcomes. Important differences were observed between the Australian and New Zealand groups including ethnic diversity with the Australian cohort having greater than 90% of parents of European descent compared to approximately 45% for the New Zealand cohort. Moreover, English was the second language for 20% of the New Zealand families. There were also important clinical differences between the cohorts, particularly notable was that the New Zealand women had higher mean HbA1c levels at recruitment reflecting poorer glucose control before intervention when compared with Australian women. In order to

Table 27.3 BSID-II divided by treatment site for MiG trial follow-up

	MDI	PDI
NZ n = 128	85	84
Australia n = 83	100	102

explore factors that were important in accounting for differences in outcome a series of regression models were built using combined New Zealand and Australian data. These analyses showed that being born to mothers of Pacific or Indian descent, having English as a second language, living in a household where adults smoked and having a birth weight over 4000 grams were all independently associated with lower scores on the MDI explaining 20% of the variability (F 8.45, $p < 0.001$, R2 0.23, Adjusted R2 0.20). Lower scores on the PDI were also associated with being born to mothers of Pacific or Indian descent, higher maternal HbA1c during pregnancy, and two recorded glucose values <2.6 mmol/l at birth. These factors explained 15% of the variability in the composite PDI scores.

Conclusions

Review of the literature regarding neurodevelopmental and cognitive development of children born to mothers with GDM leads to some tentative conclusions. Many of the reports are limited by small numbers or inadequate information on type or control of maternal DM. Furthermore, there is a complex interplay of social factors, obesity and environment that needs to be fully accounted for when assessing neurodevelopmental and cognitive outcomes in these children. Indeed one paper reported adverse effects on crude neurodevelopmental outcomes but found the effects to be no longer present after adjustment for other factors [35]. There is also a wide variety of tests used, age of assessment and impairments tested for, which adds complexity. However, the studies describing school age follow-up demonstrate a concerning pattern of lower cognitive scores, attention issues, hyperactivity and poor fine motor skills. Furthermore, the studies using data linkage analysis reinforce these concerns and raise the issue of ASD. The suggestion that a lack of difference in cognitive scores between sibling pairs favours familial characteristics over an intrauterine mechanism, which presents problems in trying to quantify concern at a population level.

With respect to the question of pharmacological treatment, it appears to be evident that, based on the follow-up of two studies reporting no differences between treatment groups [50, 51], there were no concerning effects from treatment with metformin versus insulin. This is reassuring for clinical practice but it represents only two studies and reports just the preschool population. Therefore, future work in this area is required, particularly following progress at school age and including assessment of ASD, hyperactivity and soft clinical signs on examination.

Further Work

The published work on neurodevelopmental outcomes following in utero exposure to GDM has made a significant contribution to current understanding. However, there remain a number of research gaps and further efforts are needed to fully inform policy, allow service planning and facilitate development of evidence based guidelines on long-term follow-up. Further, it may be helpful to tease out the effects of GDM exposure from other social or environmental factors. Also more work is needed to establish an evidence base for ways of improving outcomes. This includes a need for school age outcome data on contemporary cohorts of children born following pharmacological treatment of GDM. Meanwhile individual centres should understand the population of mothers and infants that they are treating and appreciate the likely supports that may be required to optimise childhood neurodevelopmental outcomes following GDM. Finally, there must continue to be efforts to reverse or slow down the epidemic of obesity and the related intergenerational effects of conditions such as GDM.

Conclusions and Recommendations

Review of the literature on childhood neurodevelopmental outcomes following maternal gestational diabetes suggests there is an increased risk of adverse outcomes. Given the fact that gestational diabetes is common and that rates are increasing it is important to ensure that children who are at risk are followed and assessed in an appropriate manner. For a child who had an uncomplicated neonatal period, screening via family doctors and agencies that provide "well child" care should be suitable. However, it is important for these groups to be aware that the pregnancy had been complicated by gestational diabetes and for their training to include education on the possible neurodevelopmental consequences. For those children who had a neonatal period that was complex and/or included major episodes of hypoglycaemia then assessment in a specialist neonatal follow-up program would be more appropriate. For some children, there may be no signs of neurodevelopmental impairment during early childhood but problems may emerge when they are required to perform more complex tasks associated with early schooling. Therefore, assessment before school entry, which is performed in many countries, may also be important. Finally, the education system should be aware of the potential effects of maternal gestational diabetes and supportive of those children who manifest difficulties.

References

1. Galtier F. Definition, epidemiology, risk factors. Diab Metab. 2010;36(6 Pt 2):628–51.
2. Duran A, Saenz S, Torrejon MJ, Bordiu E, Del Valle L, Galindo M, et al. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos gestational diabetes study. Diab Care. 2014;37(9):2442–50.
3. Lawlor DA, Fraser A, Lindsay RS, Ness A, Dabelea D, Catalano P, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia. 2010;53(1):89–97.
4. Patel S, Fraser A, Davey Smith G, Lindsay RS, Sattar N, Nelson SM, et al. Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. Diab Care. 2012;35(1):63–71.
5. Battin MR, Obolonkin V, Rush E, Hague W, Coat S, Rowan J. Blood pressure measurement at two years in offspring of women randomized to a trial of metformin for GDM: follow up data from the MiG trial. BMC Pediatr. 2015;15:54.
6. Rush EC, Obolonkin V, Battin M, Wouldes T, Rowan J. Body composition in offspring of New Zealand women: ethnic and gender differences at age 1–3 years in 2005–2009. Ann Hum Biol. 2015;42(5):498–503.
7. Kjos SL, Buchanan TA. Gestational diabetes mellitus. New Engl J Med. 1999;341(23):1749–56.
8. Reece EA, Leguizamon G, Wiznitzer A. Gestational diabetes: the need for a common ground. Lancet. 2009;373 (9677):1789–97.
9. Pedersen J. Weight and length at birth in infants of diabetic mothers. Acta Endocrinol. 1954;16(4):330–42.
10. Susa JB, Schwartz R. Effects of hyperinsulinemia in the primate fetus. Diabetes. 1985;34(Suppl 2):36–41.
11. Jansson T, Cetin I, Powell TL, Desoye G, Radaelli T, Ericsson A, et al. Placental transport and metabolism in fetal overgrowth—a workshop report. Placenta. 2006;27 Suppl A:S109–13.
12. Farrell T, Neale L, Cundy T. Congenital anomalies in the offspring of women with type 1, type 2 and gestational diabetes. Diab Med J Br Diab Assoc. 2002;19(4):322–6.
13. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed. 2013;98(1):2–6.
14. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008;122(1):65–74.
15. Watson D, Rowan J, Neale L, Battin MR. Admissions to neonatal intensive care unit following pregnancies complicated by gestational or type 2 diabetes. Aust N Z J Obstet Gynaecol. 2003;43(6):429–32.
16. Philipps AFRT, Porte PJ, Raye JR. The effects of chronic fetal hyperglycemia on substrate uptake by the ovine fetus and conceptus. Pediatr Res. 1985;19(7):659–66.
17. Philipps AFPP, Stabinsky S, Rosenkrantz TS, Raye JR. Effects of chronic fetal hyperglycemia upon oxygen consumption in the ovine uterus and conceptus. J Clin Invest. 1984;74(1):279–86.

18. Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. J Pediatr. 1992;121(1):109–14.
19. Suh SW, Fan Y, Hong SM, Liu Z, Matsumori Y, Weinstein PR, et al. Hypoglycemia induces transient neurogenesis and subsequent progenitor cell loss in the rat hippocampus. Diabetes. 2005;54(2):500–9.
20. Raman L, Hamilton KL, Gewirtz JC, Rao R. Effects of chronic hypoxia in developing rats on dendritic morphology of the CA1 subarea of the hippocampus and on fear-potentiated startle. Brain Res. 2008;1190:167–74.
21. Ramani M, van Groen T, Kadish I, Bulger A, Ambalavanan N. Neurodevelopmental impairment following neonatal hyperoxia in the mouse. Neurobiol Dis. 2013;50:69–75.
22. Jing YH, Song YF, Yao YM, Yin J, Wang DG, Gao LP. Retardation of fetal dendritic development induced by gestational hyperglycemia is associated with brain insulin/IGF-I signals. Int J Dev Neurosci Official J Int Soc Dev Neurosci. 2014;37:15–20.
23. Zornoza-Moreno M, Fuentes-Hernandez S, Carrion V, Alcantara-Lopez MV, Madrid JA, Lopez-Soler C, et al. Is low docosahexaenoic acid associated with disturbed rhythms and neurodevelopment in offsprings of diabetic mothers? Eur J Clin Nutr. 2014;68(8):931–7.
24. Stehbens JA, Baker GL, Kitchell M. Outcome at ages 1, 3, and 5 years of children born to diabetic women. Am J Obstet Gynecol. 1977;127(4):408–13.
25. Rizzo T, Metzger BE, Burns WJ, Burns K. Correlations between antepartum maternal metabolism and child intelligence. New Engl J Med. 1991;325(13):911–6.
26. DeBoer T, Wewerka S, Bauer PJ, Georgieff MK, Nelson CA. Explicit memory performance in infants of diabetic mothers at 1 year of age. Dev Med Child Neurol. 2005;47(8):525–31.
27. Nomura Y, Marks DJ, Grossman B, Yoon M, Loudon H, Stone J, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med. 2012;166(4):337–43.
28. Zornoza-Moreno M, Fuentes-Hernandez S, Prieto-Sanchez MT, Blanco JE, Pagan A, Rol MA, et al. Influence of gestational diabetes on circadian rhythms of children and their association with fetal adiposity. Diab Metab Res Rev. 2013;29(6):483–91.
29. Persson B, Gentz J. Follow-up of children of insulin-dependent and gestational diabetic mothers: neuropsychological outcome. Acta Paediatr Scand. 1984;73(3):349–58.
30. Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol. 1995;173(6):1753–8.
31. Ornoy A, Wolf A, Ratzon N, Greenbaum C, Dulitzky M. Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes. Arch Dis Child Fetal Neonatal Ed. 1999;81(1):F10–4.
32. Ornoy A, Ratzon N, Greenbaum C, Wolf A, Dulitzky M. School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. J Pediatr Endocrinol Metab JPEM. 2001;14(Suppl 1):681–9.
33. Bolanos L, Matute E, de Ramirez-Duenas M, Zarabozo D. Neuropsychological impairment in school-aged children born to mothers with gestational diabetes. J Child Neurol. 2015;30(12):1616–24.
34. Veena SR, Krishnaveni GV, Srinivasan K, Kurpad AV, Muthayya S, Hill JC, et al. Childhood cognitive ability: relationship to gestational diabetes mellitus in India. Diabetologia. 2010;53(10):2134–8.
35. Clausen TD, Mortensen EL, Schmidt L, Mathiesen ER, Hansen T, Jensen DM, et al. Cognitive function in adult offspring of women with gestational diabetes—the role of glucose and other factors. PLoS ONE. 2013;8(6):e67107.
36. Rizzo TA, Silverman BL, Metzger BE, Cho NH. Behavioral adjustment in children of diabetic mothers. Acta Paediatr. 1997;86(9):969–74.
37. Dionne G, Boivin M, Seguin JR, Perusse D, Tremblay RE. Gestational diabetes hinders language development in offspring. Pediatrics. 2008;122(5):e1073–9.
38. Deregnier RA, Nelson CA, Thomas KM, Wewerka S, Georgieff MK. Neurophysiologic evaluation of auditory recognition memory in healthy newborn infants and infants of diabetic mothers. J Pediatr. 2000;137(6):777–84.
39. Nelson CA, Wewerka S, Thomas KM, Tribby-Walbridge S, deRegnier R, Georgieff M. Neurocognitive sequelae of infants of diabetic mothers. Behav Neurosci. 2000;114(5):950–6.
40. Dahlquist G, Kallen B. School marks for Swedish children whose mothers had diabetes during pregnancy: a population-based study. Diabetologia. 2007;50(9):1826–31.
41. Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. Association of maternal diabetes with autism in offspring. JAMA. 2015;313(14):1425–34.
42. Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the avon longitudinal study of parents and children. Exp Diab Res. 2012;2012:963735.
43. Fraser A, Almqvist C, Larsson H, Langstrom N, Lawlor DA. Maternal diabetes in pregnancy and offspring cognitive ability: sibling study with 723,775 men from 579,857 families. Diabetologia. 2014;57(1):102–9.

44. Neggers YH, Goldenberg RL, Ramey SL, Cliver SP. Maternal prepregnancy body mass index and psychomotor development in children. Acta Obstet Gynecol Scand. 2003;82(3):235–40.
45. Torres-Espinola FJ, Berglund SK, Garcia-Valdes LM, Segura MT, Jerez A, Campos D, et al. Maternal obesity, overweight and gestational diabetes affect the offspring neurodevelopment at 6 and 18 months of age–a follow up from the PREOBE Cohort. PLoS ONE. 2015;10(7):e0133010.
46. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. New Engl J Med. 2005;352(24):2477–86.
47. Landon MB, Mele L, Spong CY, Carpenter MW, Ramin SM, Casey B, et al. The relationship between maternal glycemia and perinatal outcome. Obstet Gynecol. 2011;117(2 Pt 1):218–24.
48. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, Mi GTI. Metformin versus insulin for the treatment of gestational diabetes. New Engl J Med. 2008;358(19):2003–15.
49. Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. J Pediatr. 2006;148(5):628–32.
50. Ijas H, Vaarasmaki M, Saarela T, Keravuo R, Raudaskoski T. A follow-up of a randomised study of metformin and insulin in gestational diabetes mellitus: growth and development of the children at the age of 18 months. Bjog Int J Obstet Gynaecol. 2015;122(7):994–1000.
51. Wouldes TA, Battin M, Coat S, Rush EC, Hague WM, Rowan JA. Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes. Arch Dis Child Fetal Neonatal Ed. 2016.

Part VIII
Breast Feeding and Maternal Hyperglycemia

Chapter 28
Breastfeeding After Diabetes in Pregnancy: Thailand Perspectives

Sununta Youngwanichsetha

Key Points

- Breastfeeding beliefs, knowledge, and intentions of Thai women with diabetes in pregnancy influence their breastfeeding practices.
- Postpartum Thai women with a history of gestational diabetes who had low mean blood glucose levels or related complications experienced delayed lactogenesis.
- Breastfeeding duration among obese Thai women with gestational diabetes is shorter than that of overweight or normal weight women.
- Exclusive breastfeeding practice among postpartum Thai women with diabetes in pregnancy is similar as non-diabetic women.
- Breastfeeding duration among employed Thai women with a history of gestational diabetes shorter than self-employed women.
- Reproductive hormones and metabolic hormones affect lactogenesis among postpartum women with a history of gestational diabetes should be further investigated.

Keywords Breastfeeding · Lactogenesis · Infant feeding · Gestational diabetes mellitus · Thai women

Abbreviations

GDM Gestational diabetes mellitus
EBF Exclusive breastfeeding

Introduction

Breastfeeding is considered the best nutrition for newborns and infants. It provides health benefits for both the mother and their babies. Particularly, immunity in breast milk can promote child development and protect them from infectious disease. Currently, breastfeeding promotion is a global and national policy. In Thailand, breastfeeding is cultural and normative practice. It is set as a national

S. Youngwanichsetha (✉)
Department of Obstetric-Gynecologic Nursing and Midwifery, Prince of Songkla University, 15 Kanjanawanich Road, Kho Hong, Hat Yai, Songkhla, Thailand
e-mail: sununta.y@psu.ac.th; sununta.y@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_28

policy since 1989. The Ministry of Public Health followed the WHO/UNICEF Ten steps to successful breastfeeding since 1995. Baby-Friendly Hospital Initiative is administered in all hospitals and healthcare centers. The Code of Marketing of breast milk substitutes and related product was implemented since 1995. The Thai Breastfeeding Center Foundation has been established in 2004 to provide lactation education and supports for Thai women. In addition, a 90 day-paid maternity leave is offered to postpartum Thai mothers [1]. Moreover, exclusive breastfeeding is promoted, first for 4 months and currently about 6 months [2]. In addition, continuation of breastfeeding is encouraged up to 2 years to ensure appropriate child care [3]. However, the 30% target of EBF promotion is not achieved in some group of Thai women, such as mother with health problems, mothers of preterm infants. Postpartum Thai women with a history of GDM is prone to not breastfeed their newborn because of maternal and newborn complications, and lack of the right understanding regarding breastfeeding benefits on diabetes control and prevention. This review illustrates 7 essential aspects of breastfeeding practice among postpartum Thai women with a history of GDM.

Breastfeeding Belief, Knowledge, Intention, and Experience

Breastfeeding practices among postpartum Thai women with a history of GDM influence by their belief, knowledge, and intention. Most of the women have a strong belief on health benefit of breast milk for both mother and infant. The positive beliefs related to providing breastfeeding are as follows [4, 5], breast milk is the best nutritious food for infant growth and development, more convenient and cheaper than formula, in particular it enhances mother–infant attachment and bonding. The important belief of breastfeeding is helpful in the enhancement of maternal and infant bonding [6]. Thai women believe that breastfeeding is a maternal role influencing their intention, initiation, and continuation of infant feeding with breast milk [7]. In addition, Muslim Thai women believe in the benefits of breast milk and providing breastfeeding for their infants up to 2 years [8].

Their positive believes related to breastfeeding is developed through observation of breastfeeding practices among their families and others in Thai community [9]. Therefore, maternal and family beliefs related to breastfeeding should be assessed during lactation education [10]. Particularly, breastfeeding beliefs among employed postpartum mothers with a history of GDM.

Women's knowledge related to breastfeeding is provided in all healthcare centers using several media and strategies including mother–father class, healthcare personnel training, and health volunteer services. Prior studies show that Thai mothers have a high level of knowledge about breastfeeding practice [11, 12]. Adolescent Thai mothers also show high score of breastfeeding practice and could provide breastfeeding for at least 6 months [13]. Moreover, most of the Thai mothers know about breast milk extraction and preservation in refrigerator [14]. As a result, postpartum Thai women with a history of gestational diabetes mellitus had a high level of knowledge regarding breastfeeding.

Intention to give breastfeeding for their babies is planned before becoming pregnant, during pregnancy, or immediately after delivery. Prior study shows that postpartum Thai women have moderate level in EBF intention. Their breastfeeding intention is associated with knowledge, prior experience, and family support [15]. Prior report finding among postpartum Thai women show that duration of intended breastfeeding is associated with actual breastfeeding practice [16]. In contrast, postpartum mothers who planned and intended to supplement infant feeding with formula are more likely to earlier weaning breastfeeding [17].

Moreover, prior experiences of breastfeeding influence women's intension to practice infant feeding. The research evidences show that mother who breastfed their first infant are more likely to give breastfeeding for the later child [18].

Continuous Lactation Education and Supports

In Thailand, healthcare personnel, working in both government and private healthcare centers, receive continuing education or attend breastfeeding education training in order to improve their skills to provide effective breastfeeding program and lactation consultant [19]. In addition, medical, nursing, and public health students have learned to practice breastfeeding promotion [20]. The reported finding illustrates that after passing breastfeeding class, Thai nursing student demonstrate high self-efficacy score to promote breastfeeding support. Lactation education competency of medical, nursing, and other health care personnel are helpful to promote and support breastfeeding practice among postpartum Thai women with GDM. It is supported that lactation promotion education and training for medical, nursing, and other health care personnel is beneficial in providing breastfeeding support for postpartum mothers [21].

In addition, continuous lactation education and support is provided in parenting school during the antenatal, postpartum, and throughout child care.

Breastfeeding education program in Thailand also offer for father, grandmother or family significant others in order to support the mother's breastfeeding. Thai women attended the breastfeeding empowerment program demonstrate higher scores of breastfeeding behavior and longer duration of breastfeeding than those receive standard breastfeeding promotion [22]. The report finding show that 96.2% of Thai women initiate breastfeeding within 30–60 min postpartum [23].

The fathers attending breastfeeding promotion program report satisfaction with their role in support breastfeeding [24]. The reported findings show that husband support is both positive and negative impacts on maternal breastfeeding practices. Perceived strong husband support influences longer duration of breastfeeding and stronger bonding with their infants. On the other hand, mothers experience lack of husband support demonstrate shorter duration of breastfeeding [25].

In addition, the telephone follow-up visit is another method used to promote breastfeeding practice among postpartum Thai women. After discharge from hospital, Thai mothers also receive breastfeeding promotion through a telephone visit in order to follow up practice and guide to solve breastfeeding problems by lactation nurses. This strategy is helpful to help postpartum mothers to overcome breastfeeding difficulties and some problems [26]. It is supported by the clinical trial that telephone lactation counseling is effective to enhance self-efficacy and confidence in breastfeeding [27]. Another way to seek information, they can call for help from nurses and midwives providing care at all healthcare centers.

Moreover, most of the organizations provide and support baby-friendly workplace environment. Breastfeeding room or corner was prepared. The women can continue breastfeeding or express breast milk during daytime [28]. As a result, breastfeeding rates among working mothers is increased. As reported previously, breastfeeding rate among employed Thai women is 37–46.5% [29]. The reported finding an effective breastfeeding promotion implemented in Thailand is "GIFT program" comprising 4 empowerment steps: get a bright idea, improvement, feeding by family support, and that's right technique [30].

Maternal Health

Breastfeeding among postpartum Thai women with a history of GDM is also influenced by maternal health, including age, body mass index, gestational hypertension, preeclampsia, and its related complications. Maternal age influences lactogenesis and breastfeeding practices. As reported previously women aged between 20 and 30 years demonstrated early lactogenesis [31].

Lactogenesis among postpartum women with gestational diabetes might delay due to glycogen storage. The reported finding show that a common factor associated with shorter breastfeeding duration is delayed lactogenesis in phase II, longer than 72 h postpartum [32].

There are three phases of lactogenesis: phase I, phase II, and phase III. Lactogenesis phase I occurs during 10–22 weeks gestation. Phase II lactogenesis develops after giving birth and 3 days postpartum. Phase III lactogenesis begins after the third day postpartum. Maternal health associated with diabetes, obesity, insulin resistance, nutrition status, affects all phases of lactogenesis [33]. During phase II lactogenesis, prolactin and oxytocin play an important role in milk production and secretion. Several factors related to maternal health, influencing delayed lactogenesis include primiparity, maternal obesity, diabetes, hypertension, and hypothyroidism [34]. It is hypothesized that obese postpartum women have delayed lactogenesis because of insulin resistance and hypothyroid function influencing production of prolactin and oxytocin hormone [35]. As reported previously [36], obese women experience breastfeeding problems due to insufficient milk supply. In addition, one-third of postpartum women with GDM reported delayed milk production within the third day of postpartum [37].

Strict glycemic control might influence nutrition storage affecting production and quality of breast milk, colostrum, transitional and mature milk. Usually human breast milk contains lipid, protein, and carbohydrate. Mammary glands synthesize medium-chain fatty acid, three important proteins, casein, whey, and mucin, lactose and oligosaccharides from storage glycogen and macronutrients [37]. As reported previously [38], maternal illness such as diabetes has an effect on initiation and continuation of breastfeeding. The data illustrated that 30% of postpartum women with a history of GDM experience delayed lactogenesis and 44% of the mothers perceive decreased milk supply. Moreover, first-time mothers are more likely to have delayed lactogenesis and ineffective breastfeeding [39]. As reported previously, the data support that maternal illness related to diabetes influences lactogenesis, initiation, and continuation of breastfeeding. Therefore, special strategies to promote and support lactogenesis, initiation, and continuation of breastfeeding among postpartum Thai women with a history of GDM need to be the focus.

Mode of Delivery

Mode of delivery, vaginal delivery or cesarean section, affect duration between birth and first breastfeeding. As reported previously, the mean duration of first breastfeeding among women giving birth vaginally and cesarean section is 3.1 (SD = 5) hours and 10.4 (SD = 9) hours, respectively. Pregnant women with a history of GDM 69.9% give birth vaginally and 31.1% undergoes a cesarean section [40]. The previous study shows that cesarean mothers are less likely to earlier initiation of breastfeeding than normal delivery mothers (odds ratio 1.70, 95% CI 1.04–2.76) [41]. Mothers giving birth by cesarean section under general anesthesis, spinal or epidural anesthesis reported delayed formation of milk during phase II lactogenesis [42]. In addition, maternal comfort during breastfeeding might influence the initiation and continuation of breastfeeding.

Child Health Conditions

The child health condition affects initiation and continuation of breastfeeding among postpartum Thai women with a history of GDM. It is associated with gestational age, full term or preterm baby, Apgar score, latch score, and admission in intensive neonatal care units of the newborns. Infants born to mothers with GDM are at risk for development of hypoglycemia. These infants were monitored blood glucose every 2–4 h. Breast milk or colostrum is the first choice for infant feeding. The research

finding shows that infants receive colostrum are less likely to develop hypoglycemia [43]. The formula is supplemented as needed to maintain plasma glucose and prevent hypoglycemia. Mothers giving birth for term infant, usually experience complete lactogenesis phase II between 30 and 48 h postpartum, but mothers giving birth for low birth weight infant reported delayed lactogenesis, longer than 72 h postpartum. Postpartum mothers who experienced preterm birth also have delayed lactogenesis [44].

Mother's Employment

Prior studies show that mother's employment influences duration of breastfeeding. Returning to work is reported as a barrier to continue breastfeeding, though baby-friendly workplace is facilitated in some department. Postpartum Thai women with GDM who are employed and have a 90-day maternity leave discontinue their breastfeeding after returning to work (21.7%) [45]. It is similar to the study in Taiwan revealing that the women wean their infant breastfeeding earlier in order to prepare for continuation of working. For the women who are self-employed or did not return to work could continue their breastfeeding up to 18 months [46].

On the other hand, the women working in some private organizations have only 30–60-day maternity leave. Therefore, they discontinue their breastfeeding early. The previous research finding shows that postpartum mothers who plan to return to work after the first month is less likely to initiate breastfeeding and earlier weaning for their infants [47]. On the other hand, mothers who have maternity leave longer than 6 months are more likely to continue their breastfeeding [48]. Therefore, duration of maternity leave should be considered to allow at least for 6 months rather than 3 months. In addition, housewife women living in the community are more likely to continue breastfeeding to 2 years [49]. Lactation education and support should be provided for all mothers who are self-employed in order to promote their breastfeeding self-efficacy and maternal–infant bonding [50].

The summary of breastfeeding barriers and guidelines for breastfeeding facilitators for Thai women with gestational diabetes is suggested as follows (Box 1).

Recommendations

Promotion and support of breastfeeding among postpartum women with a history of diabetes in pregnancy should be planned and implemented using a breastfeeding conceptual model comprising enhancement of maternal self-efficacy, continuing of lactation education, and providing lactation support. Particularly, prior research evidences related to lactation education and support should be integrated. The proposed model of breastfeeding engagement for women after gestational diabetes is composed of three strategies: enhancement of maternal breastfeeding self-efficacy, continuing of lactation education, and providing lactation support.

- Enhancement of maternal breastfeeding self-efficacy should be promoted using an antenatal lactation preparation, metabolic health assessment and promotion, and a consideration of optimal glycemic control.
- Antenatal lactation preparation should be designed to encourage continuation of family involvement and supports.
- The metabolic health of the women with a history of diabetes in pregnancy should be assessed and promoted throughout the pregnancy and postpartum period.

Box 1 Breastfeeding barriers and guidelines for breastfeeding facilitators of Thai women with gestational diabetes

Breastfeeding barriers	Guidelines for breastfeeding facilitators
1. Delayed lactogenesis due to metabolic health and strict glycemic control	1. Assessment of metabolic health conditions, including body mass index, dietary pattern, and blood glucose records 2. The optimal target of blood glucose levels should be set and informed to the women, their family, and all healthcare providers
2. Lack of knowledge and understanding related to breastfeeding practices and benefit on plasma glucose control	1. Breastfeeding education among postpartum women with a history of GDM should be informed of recommended practice of exclusive breastfeeding for 6 months and continuing on child demand as long as for 2 years 2. Benefit of breastfeeding for maternal health should be focused on promotion of weight reduction, controlling of blood glucose, and diabetes prevention
3. Perception of insufficient breast milk production	1. The women should be educated about breast milk demand of infants 2. Promotion of breast milk production techniques should be encouraged among the women with a history of GDM 3. Metabolic health and dietary practice should be maintained to ensure sufficient nutrient supply for breast milk production
4. Difficulties and problems related to breastfeeding practice	1. Lactation education and support should be included for prevention of breastfeeding problems such as sore nipples, mastitis, and breast abscess 2. The right techniques to provide breastfeeding should be informed and monitored 3. Available resources for breastfeeding support should be informed and advised

- The women with diabetes in pregnancy should be advised about dietary pattern, doing regular exercise and blood glucose monitoring in order to achieve optimal glycemic control.
- Then, continuing of lactation education should be implemented through encouraging initiation of breastfeeding, improve breastfeeding skills, and follow-up commitment to provide breastfeeding.
- Initiation of breastfeeding should be encouraged as soon as possible, within 30 min after giving birth.
- Breastfeeding skills of the mothers with diabetes should be evaluated and improved in order to maintain their breastfeeding competency.
- Commitment to continuation of breastfeeding should be followed up during the first 6 months and for 2 years.
- Finally, providing lactation support should be monitored throughout the process of recruitment of breastfeeding supporters, continuing assessment of the difficulties in breastfeeding and solving, and maintaining of recommended breastfeeding duration.
- All available breastfeeding personnel and volunteers should be recruited to provide supports for the women to continue their lactation.
- The difficulties in breastfeeding should be assessed and promoted for effective solving throughout the breastfeeding duration (Fig. 28.1).

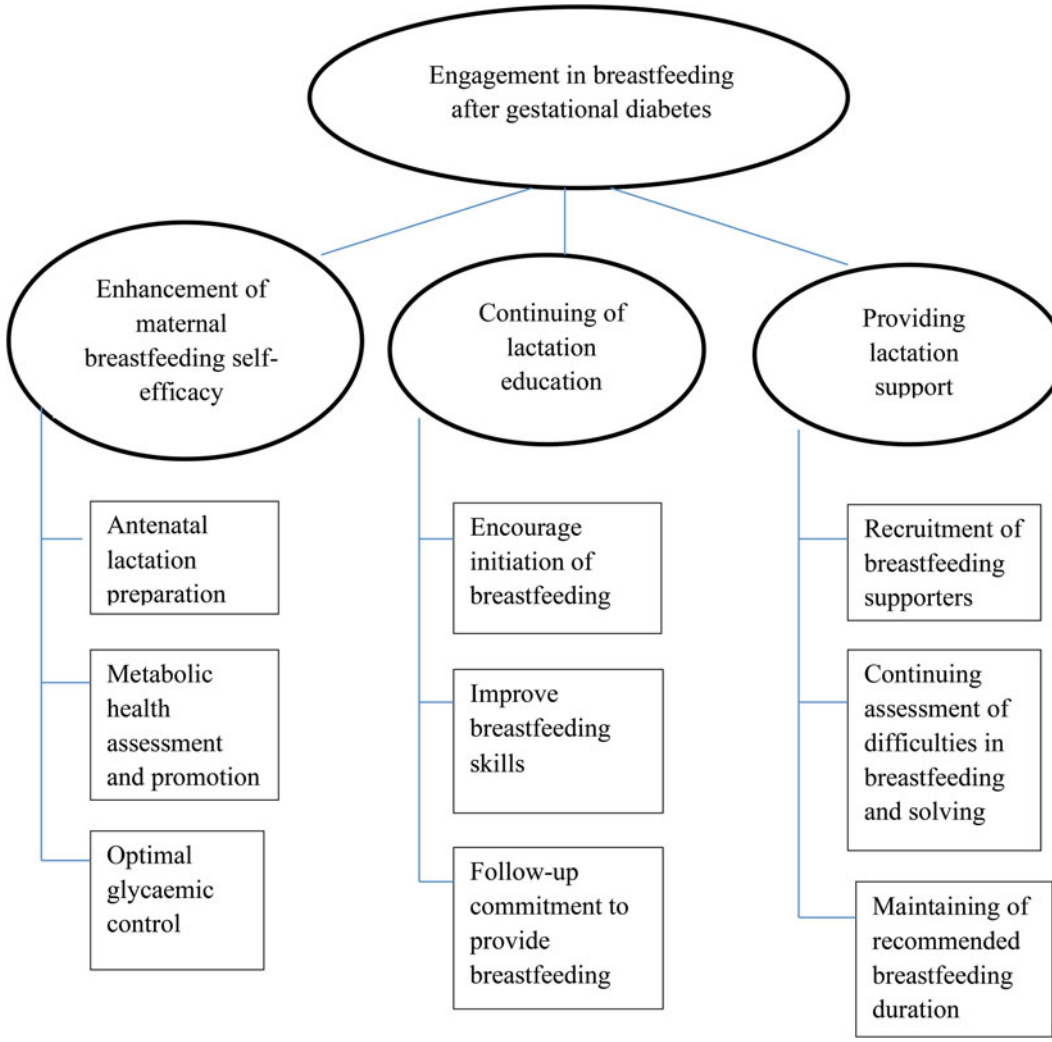


Fig. 28.1 The proposed model of breastfeeding engagement

Conclusions

Postpartum women with a history of GDM experience some breastfeeding difficulties and problems due to pregnancy complications, lactogenesis, and child health conditions. Promotion of breastfeeding practice among postpartum women with a history of GDM should focus on the appropriate glycemic control and promotion of lactogenesis. In addition, successful breastfeeding practices among postpartum women can achieve through effective lactation education and consultation.

References

1. Hangchaovanich Y, Voramongkol N. Breastfeeding promotion in Thailand. J Med Assoc Thai. 2006;89:S173–7.
2. Wangsawat T, Kaleang N, Phibal A, Jaisomkom R, Hayeese W. Factors influencing intention to exclusive breastfeeding for 6 months of mothers in Naradhiwat province. Nursing J. 2014;41:123–33.

3. Yimyam S. Breastfeeding beliefs and practices among employed women: a Thai culture perspective. In: Liamputtong P, editor. Infant feeding practice: a cross-cultural perspective. London: Springer; 2010. p. 39–54.
4. Kamolkhon V, Kamolkhon S. The factor affecting the at least 6 month feeding only by milk of postnatal mother in Nong Bua Health Center, Nongkungsri district, Kalasin province. Res Develop Health Syst J. 2014;7:57–65.
5. Mekkamol K, Deejapo J, Netgrajang C. Effect of breastfeeding promotion based on family-centered care on knowledge, attitude, of mothers and families, and exclusive breastfeeding rate for 6 months. J Phrapokklao Nur College. 2013;24:47–59.
6. Posawat N. Factor affecting breastfeeding only at least 6 month of postpartum women in Kummaung hospital, Kalasin province. Res Develop Health Syst J. 2014;7:15–29.
7. Kanhadilok S, McGrath JM. An integrative review of factors influencing breastfeeding in adolescent mothers. J Perinat Educ. 2015;24:119–27.
8. Youngwanichsetha S. Factors related to exclusive breastfeeding among postpartum Thai women with a history of gestational diabetes mellitus. J Reprod Infant Psychol. 2013;31:208–17.
9. Jagiello KP, Chertok IRA. Women's experiences with early breastfeeding after gestational diabetes. JOGNN. 2015;44:500–9.
10. Scott JA. Infant feeding beliefs and practices across cultures. In: Liamputtong P, editor. Infant feeding practice: a cross-cultural perspective. London: Springer; 2010. p. 39–54.
11. Tumchuae S, Plodpluang U. A development of breastfeeding promotion program by family support. J Prapokklao Hosp Clin Med Educat Center. 2015;32:6–17.
12. Arayasukawat P, Sukonkajorn P, Phothiraksanon P, et al. Breastfeeding practice knowledge of mothers who delivered at Srinagarind hospital. Srinagarind Med J. 2013;28:163–9.
13. Ratisunthorn J, Thaithal S, Bowanthammajak U. Effects of empowerment program on breastfeeding behavior and duration of exclusive breastfeeding among adolescent mothers. Kuakarun J Nur. 2014;21:139–54.
14. Nehring-Gugulska M, Nehring P, Krolak-Olejnik B. Breastfeeding knowledge among Polish health care practitioners supporting breastfeeding mothers. Nur Educ Pract. 2015;15:381–6.
15. Fallon A, Dunne F. Breastfeeding practices that support women with diabetes to breastfeed. Diabetes Res Clin Pract. 2015;110:10–7.
16. Kaewsarn P, Moyle W. Breastfeeding duration of Thai women. Aust Coll Midwives Inc J. 2000;13:21–6.
17. Kim E, Hoetmer SE, Li Y, Vandenbery JE. Relationship between intention to supplement with infant formula and breastfeeding duration. Can J Public Health. 2013;104:e388–93.
18. Bartick MC, Stuebe AM, Schwarz EB, et al. Cost analysis of maternal disease associated with suboptimal breastfeeding. Obstet Gynecol. 2013;122:111–9.
19. Panbangpra S, Sangperm P. Knowledge, attitude, and practice of breastfeeding promotion among nurses in private hospitals. J Nurs Sci. 2013;31:70–9.
20. Sankasuwan S, Jeanwathana J, Poonperm R. Effects of breastfeeding teaching on knowledge, self-efficacy and breastfeeding nursing care of the Royal Thai Army nursing students. J Royal Thai Army Nurs. 2013;14:133–4.
21. Nommsen-Rivers LA, Chantry CJ, Peerson JM, Cohen RJ, Dewey KG. Delayed onset of lactogenesis among first-time mothers is related to maternal obesity and factors associated with ineffective breastfeeding. Am J Clin Nutr. 2010;92:574–84.
22. Ratisunthorn J, Thaithae S, Bowanthammajak U. Effects of empowerment program on breastfeeding behavior and duration of exclusive breastfeeding among adolescent mothers. Kuakarun J Nur. 2014;21:139–54.
23. Posawat N. Factor affecting breastfeeding only at least 6 month of postpartum women in Kummaung hospital, Kalasin province. Research Develop Health System J. 2014;7:15–29.
24. Tumchuea S, Chiangta P, Sudsaguan K. Husband support towards breastfeeding during the first 6 months. J Com Dev Res. 2012;5:66–78.
25. Yuangthong S, Sawatphanit W, Deoisres W. The effect of breastfeeding promoting program for first-time postpartum mothers on breastfeeding duration and behaviors. Public Health J Burapha Uni. 2012;7:100–15.
26. Chawpreecha O, Smuntavekin S. The effect of the teaching program and telephone follow up on the behavior and duration of exclusive breastfeeding. J Nursing Siam Uni. 2014;15:37–50.
27. Tahir NM, Al-Sadat N. Does telephone lactation counseling improve breastfeeding practices?: a randomized controlled trial. Int J Nurs Stud. 2013;50:16–25.
28. Boonjan J, Chouwajaroen P, Pathumwiwatana P, Chusilp K. Development of services for promoting sustainable breastfeeding. J Nurse's Assoc Thai. 2011;29:14–24.
29. Chuang CH, Chang PJ, Chen YC, et al. Maternal return to work and breastfeeding: a population-based cohort study. Int J Nurs Stud. 2010;47:461–74.
30. Tumchuae S, Plodpluang U. A development of breastfeeding promotion program by family support. J Prapokklao Hosp Clin Med Educat Center. 2015;32:6–17.
31. Fu M, Zhang L, Ahmed A, Plaut K, Haas DM, Szucs K. Does circulation disruption play a role in the metabolic-hormone link to delayed lactogenesis II? Front Nutr. 2015;2:1–13.

32. Matias SL, Dewey KG, Quesenberry CP, Gunderson EP. Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus. Am J Clin Nutr. 2014;99:115–21.
33. Stuebe A. Association among lactation, maternal carbohydrate, metabolism, and cardiovascular health. Clin Obstet Gynecol. 2015;58:827–39.
34. Stuebe AM. Does breastfeeding prevent the metabolic syndrome, or does the metabolic syndrome prevent breastfeeding. Semin Perinatol. 2015;39:290–5.
35. Lucas R, Judge M, Sajdlowska J, Cong X, McGrath JM, Brandon D. Effect of maternal body mass index on infant breastfeeding behaviors and exclusive direct breastfeeding. J Obstet Gynecol Neonatal Nurs. 2015;44:772–83.
36. O'Sullivan EJ, Perrine CG, Rasmussen KM. Early breastfeeding problems mediate the negative association between maternal obesity and exclusive breastfeeding at 1 and 2 months postpartum. Nutr. 2015;45:2369–78.
37. Matias SL, Dewey KG, Quesenberry CP, Gunderson EP. Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus. Am J Clin Nutr. 2014;99:115–21.
38. Andreas NJ, Kampmann B, Le-Doare KM. Human breast milk: A review on its composition and bioactivity. Early Hum Dev. 2015;91:629–35.
39. Jagiello KP, Chertok IRA. Women's experiences with early breastfeeding after gestational diabetes. J Obstet Gynecol Neonatal Nurs. 2015;44:500–9.
40. Zanardo V, Svegliado G, Cavallin F, et al. Elective cesarean delivery: does it have a negative effect on breastfeeding? Birth. 2010;4:275–9.
41. Morrison MK, Collins CE, Lowe JM, Giglia RC. Factors associated with early cessation of breastfeeding in women with gestational diabetes mellitus. Women Birth. 2015;28:143–7.
42. Sankasuwan S, Jeanwathana J, Poonperm R. Effects of breastfeeding teaching on knowledge, self-efficacy and breastfeeding nursing care of the Royal Thai Army nursing students. J Royal Thai Army Nurs. 2013;14:133–4.
43. Tozier PK. Colostrum versus formular supplementation for glucose stabilization in newborns of diabetic mothers. J Obstet Gynecol Neonatal Nurs. 2013;42:619–28.
44. Parker LA, Sullivan S, Krueger C, Kelechi T, Mueller M. Effect of early breast milk expression on milk volume and timing of lactogenesis stage II among mothers of very low birth weight infants: A pilot study. J Perinatol. 2012;32:205–9.
45. Yamkarn W. Effect of developing discharge planning for mothers with diabetes mellitus during pregnancy in Obstetrics unit 3, Phrapokklao Hospital, Chanthaburi. Thailand national breastfeeding conference proceeding book; (June 5-7, 2013).
46. Chuang CH, Chang PJ, Chen YC, Hsieh WS, Hurng BS, Lin SJ, Chen PC. Maternal return to work and breastfeeding: a population-based cohort study. Int J Nurs Stud. 2010;47:461–74.
47. Aikawa T, Pavadhgul P, Chongsuwat R, Sawasdivorn S, Boonshuyar C. Maternal return to paid work and breastfeeding practices in Bangkok. Thai Asia Pac J Public Health. 2015;27:1253–62.
48. Fallon A, Dunne F. Breastfeeding practices that support women with diabetes to breastfeed. Diabetes Res Clin Pract. 2015;110:10–7.
49. Salaeh T, Doloh H. Islamic Jurisprudence on breastfeeding: a case study of Muslim families in Baget village, Khokkhian sub-district, Mueang district, Narathiwat province. Princess Naradhwas Uni J Human Soc Sci. 2014;1:20–9.
50. Busch DW, Logan K, Wilkinson A. Clinical practice breastfeeding recommendations for primary care: applying a Tri-Core breastfeeding conceptual model. J Pediatr Health Care. 2014;28:486–8.

Chapter 29
Gestational Diabetes and Peptides in Breast Milk

Suleyman Aydin

Key Points

- Breast milk contains many small, medium, and large peptide/protein hormones which influence the metabolism.
- Peptides in breast milk are reduced or elevated in response to gestational diabetes.
- The shortage or abundance of peptides in maternal milk in relation to gestational diabetes leads to endocrinal problems.
- Peptides in breast milk mediate the development of the small intestines and T-lymphocyte responses (innate immunity), as well as digestion, growth, and development of neonates.
- For the smooth running of the metabolism in neonates, peptides in breast milk must remain within the physiological range.

Keywords Gestational diabetes · Peptides · Breast milk · Metabolic balance · Nutrition · Baby

Abbreviations

ADH	Anti-diuretic hormone
AVP	Precursor of arginine-vasopressin
BMI	Body mass index
CRH	Corticotropin releasing hormone
GDM	Diabetes that develops during pregnancy
hPL	Human placental lactogen
LDL	Low-density lipoprotein
LIMA	Left internal mammary artery
NAD	Nicotinamide adenine dinucleotide
NDDG	National Diabetes Data Group
NUCB2	Nucleobindin 2
OGTTs	Oral Glucose Tolerance Tests
Oxt	Oxytocin
PACAP	Pituitary adenylate cyclase activating polypeptide
PBEF	Pre-B cell colony-enhancing factor
PRL	Prolactin
Receptor APJ	The apelin receptor

S. Aydin (✉)
Department of Medical Biochemistry and Clinical Biochemistry
(Firat Hormones Research Group), Firat University School of Medicine, Elazig, Turkey
e-mail: saydin1@hotmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_29

T2DM	Type 2 diabetes
VIS	Visfatin
WHO	World Health Organization

Introduction

An endocrinal disorder, diabetes is characterized by an elevated plasma glucose level, and its prevalence in all societies stands at around 8.5%. The term diabetes mellitus is derived from the ancient Greek word *diabainein* (meaning *passing through*) and Latin word *mellis* (meaning *sweet* or *honey*), and the symptoms of the disease were first reported three millennia ago by the Egyptians. The term diabetes, as it is currently used, was introduced by the Greek scholar Araetus of Cappodocia (81–133 A.D.,). In 1675, when the British scientist Thomas Willis added the word *mellitus* (honey sweet), the term *diabetes mellitus* was coined [1]. Diabetes mellitus is a metabolic disorder caused by a combination of both hereditary and environmental factors and characterized by extreme elevation of blood glucose level (hyperglycemia). American Diabetes Association classifies this disorder under four general headings, which are (a) Type 1 Diabetes (characterized by progressive pancreatic beta cell destruction), (b) Type 2 Diabetes (reduction of insulin receptors in target cells affected by insulin or reduced insulin efficiency at the post-receptor level in the cell), (c) gestational diabetes (impaired glucose tolerance that develops and is diagnosed during pregnancy), and (d) the other group covering cases which cannot be classified in the other three (genetic problems in the insulin pathway, enzymatic pancreas diseases, endocrinopathies, beta cell damage caused by chemical factors, and diabetes resulting from infections) [2]. Diabetes mellitus during pregnancy has a complication rate of 3–14% [3, 4], and in the range of 3–5% in North America and Europe [5]. This chapter will exclusively focus on gestational diabetes mellitus and peptides in breast milk.

The Content of Breast Milk

Although at least 88% of it consists of water [6], breast milk also contains other nutrients that are required for optimal growth and development, such as energy elements (lactose, fat), minerals (sodium, potassium, calcium, phosphorus, chlorine, magnesium, iodine, iron, copper, zinc, selenium, taurine, sulphur), vitamins (beta carotene, retinol, vitamins C, D, E, K, thiamine, riboflavin, B12, nicotinic acid, folate, B6, biotin, pentanoic acid), proteins (casein and whey [lactalbumin, lactoferrin, lysozyme, immunoglobulins, albumin], casein/whey ratio is 40/60), cytokines [7], and peptides (over 100) [8]. Thus, breast milk is an easy to digest natural food with high bioavailability [8]. Lactose aside [6], the main energy-giving element in breast milk is fats derived from both fat in the diet and that in the mother's fat reserves (adipose tissue). As of the present day, it is known that adipose tissue secretes more than 600 peptide/protein-structure adipokines.

The Fate of Breast Milk Peptides/Proteins in Gestational Diabetes

The dramatic advances made in the fields of molecular biology and molecular biochemistry in recent years have led to the discovery of many peptides and proteins responsible for the metabolic regulation. The peptides/proteins in biological materials and their discovery year and methodology were seen in

Table 29.1 The peptides/proteins were first discovered in Biological materials and their discovery year and methodology

Hormones	Biological materials where they were first discovered				Milk (first discovered)	
	Tissue/cell	Method	Receptor	Year	Method	Year
Adropin (43 aa)	Liver	Microarray, *In situ* hybridization	G protein-coupled	2008	ELISA	2013
Apelins (changeable)	Stomach	RT-PCR, HPLC	APJ	1998	ELISA	2010
Hepcidins (changeable)	Blood ultrafiltrate	Mass spectrometry	Ferroportin	2000	ELISA	2013
Salusins (α20 aa;β 28aa)	cDNA library	Silico analysis	unknown	2003	ELISA	2013
Copeptin (39 aa)	Neurohypophysis	Gel filtration, chromatography, electrophoresis	CPR	1972	ELISA	2012
Preptin (34 aa)	TC6-F7 beta cells	RIA, IHC	Unknown	2001	ELISA	2013
Obestatin (23 aa)	Stomach	Isolation	GPR39	2005	ELISA	2008
Oxytocin (9aa)	Pituitary gland	Isolation	OXTR	1906	RIA	1986
PACAP (39aa)	Ovine hypothalamic	Isolation	PACAPR	1989	RIA	2009
Motilin (23 aa)	Small intestine	Purification	MTLR	1973	ELISA	1994
Ghrelins (28 aa)	X/A (ghrelin) cell	RIA, ELISA	GHS-R1a	1999	RIA, ELISA	2006
Insulin (51 aa)	Pancreas	Isolation	IR	1920	RIA	1975
Nesfatin-1 (82 aa)	Hypothalamus	*In situ* hybridization	NUCB2	2006	ELISA	2010
Irisin (112 aa)	Muscle cell	Western Blot	Unknown	2012	ELISA	2013
Leptin (146 aa)	Adipose		Ob-receptor	1994	RIA, ELISA	1997
Visfatin (491 aa)	COS 7 and PA317 cells	cDNA library	Insülin?	1994	ELISA	2012
Prolactin (198 aa)		Purification	PRLR	1969	RIA	1975
Resistin (108 aa)	Small intestine epithelium, bronchus epithelium and white fatty tissue	Sequence analysis IHC, electrophoresis, Western blot, Northern blot	Adenylyl cyclase-associated protein 1	2001	RIA, ELISA	2008

Table 29.1. As it is known, there are many studies suggesting that impaired glucose tolerance in gestational diabetes is associated with the reduced or elevated synthesis of small, medium, and large peptides and proteins during pregnancy. The changes caused by gestational diabetes in the quantities of peptides and proteins in the maternal circulation also alter the amounts of peptide- and protein-structure molecules in breast milk. However, when peptide and protein molecules in breast milk do not fall within the physiological range, many pathological events will occur. The small, medium, and large peptides and proteins in breast milk serve a multitude of biological functions (Table 29.2). These biological functions will be explained in detail in the context of each peptide and protein. In the following parts of the book,

Table 29.2 Major biochemical functions of the peptides/proteins found in breast milk

Peptides/proteins	Alteration with GDM	Major functions
Small peptides		
Adropin	↑ (11), ↓ (8,12)	Glucose homeostasis
Apelins	↓ (17)	Inhibition of insulin secretion
Copeptin	↑ (8)	Contributes to the 3D folding of vasopressin
Ghrelins	↓ (25,26)	Starts feeding, regulates glucose metabolism and GH release
Hepcidins	↑ (32)	Regulator of iron metabolism, anti-microbial
Motilin	–	Peristalsis in the small intestine and clears out the gut
Obestatin		Regulation of energy balance
Oxytocin		Milk ejection, uterine contraction, maternal, and social behavior
PACAP		Parasympathetic and sensory neurotransmitter
Preptin	↑ (29)	Regulation of insulin secretion and glucose metabolism
Salusins	↓ (29)	Hypotensive, anti-microbial
Medium peptides		
Insulin	↑ (9)	Control of blood glucose and preventing hyperglycemia
Nesfatin-1	↓ (17)	Regulation of food intake and anti-hyperglycemic
Large peptides		
Irisin	↓ (8,66)	Regulation of fat and glucose metabolism
Leptin	–	Satiety signal, regulator of fertility, appetite, and food intake
Prolactin		Lactation and maternal behavior
Resistin	↑ (82)	Insulin resistance, inflammation, and obesity
Visfatin	↑ (90)	Regulation of pancreatic beta cell functions

GH Growth hormone. *PACAP* Pituitary adenylate cyclase activating polypeptide. *GDM* Gestational diabetes

the fate and biochemical effects of peptides and proteins in breast milk in gestational diabetes will be explained under the following titles: The fate and biochemical effects of small peptides (containing fewer than 50 amino acids); the fate and biochemical effects of medium-size peptides (containing 50–99 amino acids); and the fate and biochemical effects of large peptides (containing more than 100 amino acids), where the concerned peptides will be presented in alphabetical order (Figure 29.1).

The Fate and Biochemical Effects of Small Peptides

Adropin

Containing 43 amino acids, adropin has a molecular weight of 4.999 kDa [9]. It was first discovered to be synthesized in the liver and brain tissues by Kumar et al. [10]. Recent immunohistochemical studies have revealed that adropine is synthesized in almost all biological tissues and its amount in biological tissues increases with gestational diabetes. Its circulating amount varies depending on the metabolic stress in organisms [11]. When mice with diet-induced obesity are given adropine and in transgenic mice which characteristically have excessive adropine synthesis, a remarkable decrease is seen in glucose intolerance and insulin resistance [10]. Glucose intolerance and insulin resistance are two main factors that are involved in food intake and maintenance of metabolic homeostasis. Adropin amounts were reported to decrease significantly in both type 2 diabetes patients and the maternal serum and cord blood of pregnant women with GDM [12]. Aydin et al. [8] were the first to show the

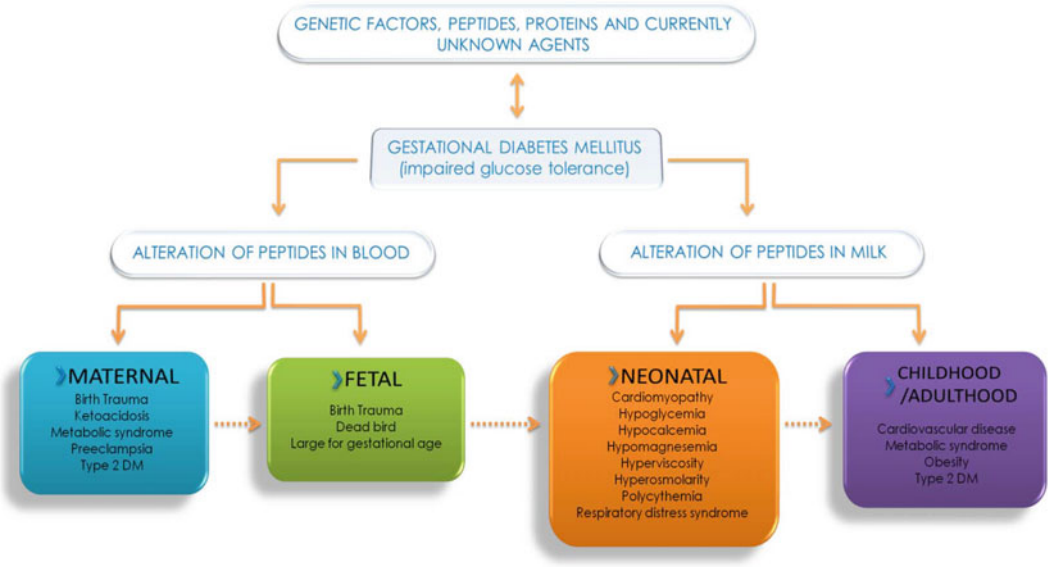


Fig. 1 Interactions between and biochemical and physiological effects of various peptides that alter the glucose metabolism in gestational diabetes

presence of adropine in colostrum, transitional, and mature breast milk and reported that adropine dropped significantly in both plasma and breast milk in GDM. Currently, it is not known if the adropine found in breast milk originates from the plasma, mammary tissue or both.

Apelins

It was discovered in 1993 that apelin was the endogenous ligand of the "orphan" (The apelin receptor: receptor APJ) [13]. Five years after this discovery, Tatemoto et al. [14] reported that a substance they found in the bovine stomach juice acted by activating the G protein-coupled APJ receptor and called this substance in peptide structure apelin. Apart from the stomach juice, apelin is synthesized in many peripheral organs including the central nervous system in particular, and heart, lungs, and mammary tissue, where its receptors are found. Apelin gene is located on Xq25-26.1 chromosome and originates from a preproapelin precursor with 77 amino acids. Synthesized preproapelin is then converted through post-translational mechanisms into forms with varying numbers of amino acids (like apelin-10, apelin-11, apelin-12, apelin-13, apelin-15, apelin-17, apelin-19, and apelin-36). All of these forms of apelin are biologically active [15]. Apelin mediates glucose intake to the cells and elevates insulin sensitivity. In cases of weight loss induced by diet or bariatric surgery, circulating amounts of apelin are reduced, while patients with obesity, morbid obesity, impaired glucose tolerance, and type 2 diabetes (T2DM) have high apelin values [16]. The presence of apelin-36 and apelin-12 was discovered in types of breast milk (including colostrum, transitional milk, and mature milk) in 2010, and it was reported that amounts of apelin-36 and apelin-12 decrease in breast milk and maternal serum in GDM. Currently, it is not known whether breast milk contains other forms of apelin and how their fate changes in GDM [17]. Likewise, it is unknown if apelin-36 and apelin-12 found in types of breast milk originate from the plasma or mammary tissue. However, since their molecular weight and number of amino acids are both low, it is probable that apelins pass to the breast milk from the plasma. Still, since mammary tissue has apelin immunoreactivity, if apelin does not pass to the tissue from the plasma through saturation, then the only source of apelins may be the

mammary tissue [17]. Reduced amounts of apelin in the maternal circulation and breast milk may impair a number of biological functions. As apelins are multi-functional peptide molecules, they have many biological effects such as the regulation of blood pressure (reducing systolic and diastolic blood pressure), regulation of the fluid and electrolyte balance (mediation of the reabsorption of water), regulation of food intake, and the effect on the respiratory system (when in excess, it causes respiratory apnea) [15]. If the mother's apelin levels can be kept in the physiological range over the duration of pregnancy and if the apelin level in maternal milk remains in the physiological range after birth, many complications listed above can be avoided.

Copeptin

Discovered in 1986, copeptin is a glycoprotein molecule consisting of 39 amino acids. It forms the C-terminal part of the pre-provasopressin molecule, which is a precursor of arginine-vasopressin (AVP = ADH = anti-diuretic hormone) and contains 164 amino acids [18]. It is released in response to pathological events such as exercise, hypoglycemia, hypoxemia, stroke, and infection. Its release is stoichiometrically equivalent to the release of ADH molecule. It is synthesized in the hypothalamus and pituitary glands [19]. Besides its physiological effects such as altering the osmotic pressure and reducing blood pressure, its role(s) in biological systems is not known yet. As the ADH molecule (composed of 9 amino acids) is very short and has a very short half life, it is very difficult to be measured. Thus, to find out the ADH amount in the circulation, copeptin amounts are measured. Patients with diabetes insipidus have low mean copeptin and ADH levels [20]. Copeptin was first identified by Aydin in breast milk in 2013 [8]. Then, Fırat hormone research group led by Aydin explored how the fate of copeptin changed in the circulation, and colostrum, transitional and mature milk of mothers with gestational diabetes using ELISA method. They found that colostrum contained more copeptin than transitional and mature milk samples. They also reported that copeptin levels in the samples collected during colostrum, transitional, and mature milk periods from mothers with gestational diabetes were higher than those in control samples and were parallel to the circulating levels of copeptin in these mothers [8]. The origin of copeptin discovered in breast milk is not known, neither its function. However, since its release is stoichiometically equivalent to that of ADH, it can give an idea about the water reabsorption in infants or their disposition to diabetes insipidus. Additionally, it may be contributing to the regulation of the metabolic pathways or postnatal growth and organ development in infants. Its normal concentration ranges between 6.5 and 7.5 ng/ml in blood and 6.1 and 7.8 ng/ml in milk [8].

Ghrelins

This hormone with 28 amino acids and a molecular weight of 3.370 kDa was discovered in 1999 by Kojima et al. [21]. Its most salient feature is being the only peptide hormone that contains a fatty acid. Ghrelin is found in four different forms in the biological fluids and tissues. The first form is the one which has an octanoic acid bound to the third serine amino acid on its N-terminus (in frogs, serine is replaced by threonine). In the second form of ghrelin, n-decanoil fatty acid is bound to the third serine amino acid. The third form of ghrelin is the one where n-decanoil fatty acid (containing a double bond) is bound to the third serine amino acid at the N-terminus. The fourth and the last form is the desacyl one that does not contain any fatty acid, and is the most commonly found ghrelin form in circulation [22]. Biologically, the most active ghrelin forms are acylated ones. The major biological function of ghrelin is stimulating feeding, and it is thus called the "hunger hormone." Acylated forms of ghrelin, especially octanylated forms, are responsible for the release of the growth hormone. The hormone was first shown to be synthesized in the X/A cells of stomach (ghrelin cells). Later studies demonstrated that it was

synthesized in almost all biological tissues, including the mammary tissue [22]. Researchers usually study the octanylated form containing eight carbons and desacyl form of ghrelin [9, 22]. The presence of acylated and desacyl ghrelin in maternal milk was revealed by Aydin and colleagues in 2006 [23]. Later, Kierson et al. confirmed their results by measuring total ghrelin amounts in breast milk. The sources of ghrelin identified in maternal milk by researchers are the plasma and mammary tissue [24]. Since ghrelin controls the glucose metabolism, the changes of octanylated and desacyl ghrelin in colostrum, transitional and mature milk of mothers with gestational diabetes were examined and it was reported that ghrelin amounts both in maternal serum and those types of milk were reduced in gestational diabetes [25, 26]. The presence of other forms of ghrelin in breast milk has not been studied yet. Reduced ghrelin levels in maternal milk due to gestational diabetes may pave the way for growth retardation, loss of appetite in babies and to obesity and type 2 diabetes later in life. That is because when ghrelin drops below the physiological limits, it cannot fulfill its endocrinal functions. Given that ghrelin is released from the stomach, and therefore is resistant to acids, ghrelin taken from the oral route (through maternal milk) regulates appetite and mediates food intake [9]. The concentration of ghrelin in milk ranges between 70 and 4000 pg/mL [22, 23].

Hepcidin

Discovered in 2000, this peptide is synthesized primarily by the liver [27]. Salivary [28] and mammary glands [29] have hepcidin immunoreactivity. It was reported to be synthesized in myeloid cells as well, against bacterial pathogens [30]. Its gene is the HAMP gene located on chromosome 19. Synthesized as a preprohormone with 84 amino acids, it is then converted to its prohormone forms with 60 and 25 amino acids; it also has 20- and 22-amino-acid forms in the urine. The conversion of prohepcidin to hepcidin is mediated by prohormone convertase furin regulated by alpha-1 antitrypsin. Ferroportin, a basolateral transmembrane protein, is the receptor of hepcidin [31]. Hepcidin receptor is found in the placenta, intestines, reticuloendothelial macrophages, and hepatocytes. The major role of hepcidin is to reduce iron absorption from the small intestines, prevent iron release to the plasma, and coordinate the use and storage of iron [31]. Hepcidin also has an anti-microbial characteristic [30]. Additionally, recent studies have shown that prohepcidin is associated with impaired glucose tolerance and insulin resistance. Studies including diabetic subjects, including those with gestational diabetes mellitus all reported elevated levels of hepcidin [32]. In 2013, Aydin et al. [29] were the first to identify prohepcidin and hepcidin-25 in breast milk (colostrum, transitional milk, and mature milk) using ELISA method. Hepcidin levels in the colostrum, transitional milk, and plasma of mothers with gestational diabetes were established to be significantly higher than those in the control subjects. However, plasma prohepcidin and hepcidin-25 levels in the mature milk period were found lower. The authors also reported that mammary glands had hepcidin immunoreactivity [29]. Therefore, hepcidin in breast milk may be coming from two sources. Hepcidin, after reaching its plasma saturation, may be transferred to breast milk through diffusion or hepcidin synthesized in the mammary tissue may directly go into milk. Elevated circulating hepcidin in gestational diabetes may be a compensatory mechanism aimed to reduce iron absorption from the small intestines, as free iron that is formed in cases of iron excess causes inflammation by enabling the production of free oxygen radicals as a pro-oxidant [33]. However, since it is an anti-microbial molecule, hepcidin can also protect the neonate against various pathogens [30]. Consequently, hepcidin is like a double-edged sword; both its deficiency and excess cause problems, and that is why it has to remain in the physiological range. The normal concentration of hepcidin in the blood changes between 460 and 610 pg/ml, while its normal concentration in breast milk ranges from 510 to 575 pg/ml [29].

Motilin

This peptide was isolated from the duodenum by Brown et al. [34] in 1971. It consists of 22 amino acids and has a molecular weight of 2.698 kDa. Increasing gastrointestinal motility, this hormone stimulates the release of pepsin, somatostatin, and pancreatic polypeptide. Motilin in breast milk (0.443 ng/ml) was first identified by Yang et al. [35] in 1994. This concentration identified by the researchers corresponds to half of the motilin amount found in the circulation. Although diabetic individuals with upper gastrointestinal tract dysmotility are known to have altered motilin levels [36], it has not been studied how motilin levels change in the milk of mothers with gestational diabetes. Likewise, the physiological significance of motilin in maternal milk is unknown, but it is believed to mediate the easy defecation of the infant and the acquisition of intestinal habits, as breastfeeding mothers have elevated motilin levels [9].

Obestatin

Discovered in 2005 by Zhang et al. [37], obestatin is composed of 23 amino acids and has a molecular weight of 2.516 Kda. Originating from pre-pro-ghrelin this peptide with an anorexigenic character antagonizes the effects of ghrelin. Obestatin has many biological functions, including the inhibition of thirst, improvement of memory, regulation of sleep, enhancement of cell proliferation, elevation of exocrine pancreas secretion, regulation of energy balance, regulation of glucose metabolism, reduction of food intake, gastric emptying, regulation of body weight, inhibition of intestinal motility, inhibition of somatostatin and pancreatic polypeptide release, regulation of insulin resistance, longevity of pancreatic beta cells, elevation of glucagon release, and inhibition of insulin secretion induced by glucose. Individuals with diabetes and impaired glucose tolerance have been reported to have reduced amounts of obestatin [38]. The presence of obestatin, which is associated with insulin amounts and insulin sensitivity, in breast milk was first shown by Aydin et al. [26] in 2008. In their study, the authors reported that levels of obestatin in colostrum and mature milk doubled in comparison to the obestatin levels in blood over the same periods. The presence of obestatin in maternal milk was then confirmed by an independent group of researchers [39]. However, there is no study examining how the amounts of obestatin, associated directly with insulin amounts and insulin sensitivity, change in the milk of mothers with gestational diabetes. Although the origin and the role in infant development of obestatin is not certain yet, it has been suggested that obestatin inhibits the appetite to enable the gastrointestinal system of the neonate to get accustomed to milk (food) in the early stages of its life and mediates the metabolic regulation of neonates in collaboration with the appetite increasing ghrelin.

Oxytocin (Oxt)

A hormone with a molecular weight of 1007 daltons and composed of nine amino acids, oxytocin was discovered in 1906 [40]. Its amino acid sequence has been well-preserved in mammals with a placenta over the evolutionary process. Released by the posterior pituitary gland, the principal function of oxytocin is to induce birth by causing uterus contractions. Additionally, it mediates the stoppage of bleeding. In non-pregnant women, it helps the contraction of vagina to let the sperm in [41]. Oxytocin was discovered for the first time in maternal milk in 1986 by Takeda et al. [42] using RIA method. Currently, there is not any literature study investigating how oxytocin amounts in breast milk change with gestational diabetes. However, a study comparing normal pregnant women with those having gestational diabetes reported that there was no difference between their serum oxytocin levels [43]. While normal oxytocin level in breast milk was found to be 3.1 $\pm$ 0.6 mu/ml, this level

rises up to 5.3 ± 1 mu/ml when the baby starts nursing [9]. Oxytocin in maternal milk is quite stable and passes from maternal blood to milk, from where it is transferred to the infant. Even though it is currently not known what function oxytocin serves, it may be involved in the establishment of an emotional bond between the mother and the infant, as oxytocin is also known as the "love hormone" and the hormone of obedience. It can also help reduce fear and anxiety in babies, as well as alleviating depression, as oxytocin possesses an anti-depressant-like effect [41]. It is yet to be known if there is a relation between its amounts during the puerperal period. Additionally, oxytocin in breast milk may mediate the reduction of disposition to autism, since oxytocin was reported to produce significant improvement in the behaviors of autistic children [44]. Consequently, these data indicate the importance of nursing.

Pituitary Adenylate Cyclase Activating Polypeptide (PACAP)

Isolated in 1989 by Miyata et al. [45] from ovine hypothalamic extracts, PACAP consists of 38 amino acids. It has two biological forms in biological tissues and fluids, which are PACAP-38 with 38 amino acids and C-terminally truncated 27-amino-acid form [45]. This peptide molecule is synthesized outside the brain, as well as in the peripheral organs including the pancreas, gonads, respiratory, and urogenital tracts [45]. In humans and rodents, PACAP is localized in the secretory vesicles of the pancreas where insulin and glucagon are also localized [45]. PACAP has been reported to act as a neurotransmitter, neuromodulator, and neurotrophic factor [46], as well as in preventing complications associated with diabetes [47]. The presence of this peptide in maternal milk was first demonstrated in 2009 by Borzsei et al. [48] using RIA method. The authors also reported that the amounts of PACAP in breast milk were higher than those in blood. Although PACAP is known to alleviate complications associated with diabetes, there is currently no study exploring how its fate changes in the milk of diabetic mothers. Likewise, the function of pituitary adenylate cyclase activating polypeptide is not certain. However, it is speculated that the pituitary adenylate cyclase activating polypeptide in breast milk would have paracrine and autocrine effects on the biological systems of infants, as it does in the maternal circulation [9], and it is believed that PACAP contributes to glucose regulation in infants [47].

Preptin

Preptin was isolated from murine βTC6-F7 β-cells by Buchanan et al. in 2001. Having 34 amino acids and a molecular weight of 3.948 kDa, this molecule is formed by splitting from Asp^{69}-Leu^{102} of the proinsulin-like growth factor II E [49]. Although it was initially discovered to be synthesized in the pancreatic beta cells, preptin was later established to be a tissue peptide synthesized in a number of organs, including the salivary gland [11]. Since exogenous preptin administration causes glucose-mediated biphasic insulin secretion, it is certain that preptin concentrations are correlated with diabetes [50, 51]. In this framework, Aydin et al. [29] examined preptin amounts in the milk and blood of diabetic mothers and reported that preptin levels in both the serum and breast milk were elevated in relation to gestational diabetes. Besides, betatrophin secreted from pancreatic beta cells is also found in maternal milk and the levels of this peptide increase in gestational diabetes as well (manuscript in preparation). Currently it is not certain whether preptin and betatrophin in breast milk originate from the plasma or mammary gland. However, since both peptides have low numbers of amino acids, they can pass to milk through the plasma, or they may be produced by the mammary gland. These peptides may mediate glucose homeostasis of the infant and the secretion of insulin in

amounts that will meet the needs of the organism. Normal serum values are 8.64 ± 1.16 ng/ml for preptin and 8.9 ng/ml for betatrophin, while normal breast milk values are 8.9 ng/ml for preptin and 10.2 ng/ml for betatrophin [30].

Salusins

Having two forms as salusin-alpha (with 28 amino acids) and salusin-beta (with 20 amino acids), salusins were discovered in 2003 by Shichiri et al. [52] who used human full-length enriched cDNA library in their bioinformatics analyses. Later, the presence of salusins was shown in the nervous system, cardiovascular system, kidneys, monocytes, macrophages, stomach, small intestines, liver, medulla, thymus, lymph nodes, bone marrow, spleen, human aorta, "left internal mammary artery (LIMA)," saphena, plasma, urine [53], and milk [29]. Their major biological function is the regulation of blood pressure [52, 53]. Additionally, salusin-beta was reported to have an anti-microbial activity against gram-positive bacteria [54]. Circulating levels of salusins are lowered in diabetes [12]. Aydin et al. [29] identified the presence of salusins in breast milk, including colostrum and transitional milk, with ELISA method in 2013 and reported that mammary glands synthesized salusins. Salusin-alpha and salusin-beta levels in the breast milk and plasma were reported to decrease significantly in gestational diabetes relative to the levels in control breast milk and plasma [29]. The origin of salusin-alpha and salusin-beta in breast milk is not known for sure. It is assumed that they may have originated from the blood due to plasma saturation, released to the milk from mammary tissue, or both. Likewise, the function of salusins in breast milk is not certain. However, it has been suggested that salusins may be involved in the regulation of the cardiovascular system of infants and that salusin-beta in particular might be protecting the neonate against gram-negative bacteria [54].

The Fate and Biochemical Effects of Medium-Size Peptides

Insulin

A polypeptide hormone with 51 amino acids and a molecular weight of 5.8 kDa [9]. Insulin serves in the regulation of the carbohydrate mechanism by reducing the glucose amount in organisms [55]. Insulin, derived from the Latin word *insula*, meaning island, is secreted from Langerhans (named after the German physician Paul Langerhans) islets in the pancreas. Discovered by Fredrick Banting in 1922, insulin has a biological half life of 5–7 min [9, 56, 57]. Its normal plasma level ranges from 3 to 20 mIU/ml in fasting and between 16 and 166 mIU/ml in satiety [55]. Insulin in breast milk was discovered in 1975 by RIA method, and its amount was reported to vary between 12–19 and 56 μIU/ml [9, 58]. Insulin levels in the milk (including colostrum and transitional milk) of diabetic mothers were found higher than those in control mothers from the third postnatal day to the third month. Although not synthesized by the mammary tissue, insulin passes actively to milk and its function is not certain. However, researchers have reported that it is functionally involved in the development of the infant. Besides, insulin in maternal milk was found to reduce the glucose levels in infants [59, 60]. Consequently, since mothers with GDM have higher insulin levels in breast milk, their babies are at risk for developing hypoglycemia, and medical personnel should be aware of this risk [9].

NUCB2/Nesfatin-1

Composed of 82 amino acids and with a molecular weight of 9.552 kDa, this hormone was discovered in 2006 by Oh-I et al. [61]. Since analyses in biological fluids have shown that nesfatin-1 is cross-reactive with nucleobindin 2 (NUCB2), from which it is derived, it is suggested that it should more properly be called NUCB2/Nesfatin-1, and that is how it will be referred to here. Apart from nesfatin-1, it also has nesfatin-2 and nesfatin-3 forms; however, since NUCB2/Nesfatin-1 is responsible for appetite and regulation of fat formation in the body, studies up to the presented have focused on Nesfatin-1. NUCB2/Nesfatin-1 is a tissue hormone produced by many organs, including the lateral hypothalamic area, hypothalamic paraventricular nucleus, arcuate nucleus, supraoptic nucleus, nucleus tractus solitarius and spinal cord, stomach, pancreas, skeletal muscles, liver, subcutaneous and visceral fat tissue, brown adipose tissue, and salivary glands [62]. NUCB2/Nesfatin-1 levels drop in type 2 diabetes mellitus. Besides type 2 diabetes mellitus [63], it is associated with a number of metabolic diseases. NUCB2/nesfatin-1 in maternal milk was first demonstrated by Aydin and colleagues [17]. The authors reported that NUCB2/Nesfatin-1 levels were reduced in gestational diabetes and that serum, colostrum, and mature breast milk NUCB2/Nesfatin-1 amounts were positively correlated [17]. Currently, it is not certain whether NUCB2/Nesfatin-1 originates from the blood or synthesized by mammary gland, or both. Likewise, the role of NUCB2/Nesfatin-1 in the infant's metabolism is not known yet. Its normal concentration has been reported to be 1.2 ± 0.4 ng/ml in milk and 0.98 ± 0.3 ng/ml in blood [17].

The Fate and Biochemical Effects of Large Peptides

Irisin

Irisin, a molecule composed of 112 amino acids and having a molecular weight of 12.587 kDa, was found to be produced by the skeletal muscle by Boström et al. [64]. Since it was initially shown to be synthesized by muscle cells, irisin was included into the class of myokines. However, later immunohistochemical studies reported that it had immunoreactivity in almost all biological system tissues [11] and all blood cells, except erythrocytes [65]. The primary biological role of irisin is to mediate the conversion of white adipose tissue to brown, and in the brown adipose tissue, to increase the amount of uncoupling protein amount, thus preventing ATP formation and leading to heat release [65]. Through this mechanism, irisin increases the total energy consumption of organisms and prevents the development of obesity and diabetes, while mediating the reduction of insulin resistance [11]. A total of 23 different (cross-sectional and six-case controlled) studies registering 1745 diabetic and 1337 non-diabetic cases compared irisin levels and reported significantly lower levels of blood irisin in type 2 diabetes and gestational diabetes patients, with the exception of Asian group studies [66]. The presence of irisin in maternal milk was first reported in 2013 by Aydin et al. [8] who reported that irisin levels decreased in the milk and blood of patients with gestational diabetes. Irisin in breast milk probably stems from mammary glands (which have irisin immunoreactivity), but it may also be passing to the milk after being saturated in the blood. The biological function that irisin in maternal milk serves for infants is not known yet. However, it can be said that its functions in infants are the same as the ones it serves in mothers, that is, burning fat, producing heat, contributing to thermo-regulation, and providing protection against obesity [11], and even cancer, as studies on cancer cell lines reported that irisin prevented the proliferation of cancer cells [67]. Considering that irisin levels are elevated in exercise and the prevalence of cancer is 35–40% lower in those who exercise, irisin will inevitably protect the baby against cancer [68]. The normal concentration of irisin as measured by LC-MS/MS is 4.6 ng/ml [69]. Currently ELISA method is preferred in the

measurement of peptides, as it is practical and easy to use [70]. ELISA measurements of irisin show that (although the values change depending on the measurement kits used) normal irisin concentrations range between 550 and 600 ng/ml in blood and between 600 and 750 ng/ml in maternal milk.

Leptin

Leptin, a product of the obesity gene, was discovered in 1994 by Zhang et al. [70]. Its main producer is the adipocytes, while a number of biological tissues like the stomach (the lower part of the fundic glands), heart, ovaries, bone marrow, skeletal muscle, and mammary epithelial cells also produce small amounts of leptin [71]. Since leptin is produced by the placenta as well, its amounts increase in pregnancy and fall after birth. The fact that adipocytes did not only serve as fat stores, but was an active organ producing several hormones was first revealed through the discovery of leptin [72]. After this discovery, molecules synthesized by and released from fat cells came to be referred to as adipokines [71]. In humans, leptin gene is located on the seventh chromosome [73]. Leptin has a molecular weight of 16 kDa and consists of 167 amino acids. However, non-glycosylated mature leptin found in the circulation is composed of 146 amino acids [9, 70]. The presence of leptin in human milk was found by Casaibell et al. [74] in 1997. The major role of leptin is to send information to the satiety/hunger center in the hypothalamus of the brain about the fat reserves of the body. If the organism's fat reserves are full and there is no resistance against leptin, our brain suppresses our appetite [71]. Normal leptin concentrations vary between 0.1 and 0.5 ng/mL in males and stand at 1.3 ng/mL in females [9], while its normal concentration in breast milk ranges from 0.35 to 4.6 μg/L [74]. As leptin has receptors in gastric epithelial and small intestinal absorptive cells, it has been suggested that the leptin in maternal milk may be transferred to the infant and be involved in the regulation of nutrition. Absorption of leptin by the immature stomach and especially leptin transfer to the infant's circulation in the early phases of lactation period is believed to have a part in weight control in later years of life [75].

Prolactin (PRL)

Prolactin was identified in humans by Friesen et al. [76] in 1970. Up to the present day, three prolactin molecules with three different molecular weights, called little prolactin (22 kDa), big prolactin (48 kDa) and big prolactin (150 kDa), have been reported. Of these prolactins, only the little prolactin with 198 amino acids is the biologically active form and it is also the most commonly found prolactin in circulation. Other prolactins have almost no biological activity [77]. Prolactin is mainly responsible for releasing milk and contributes to the development of the immune system, metabolic regulation, and the development of the pancreas [9]. Its presence in maternal milk was shown in 1975 with RIA method [78]. Prolactin concentrations in breast milk are similar to those in the plasma. Prolactin concentrations in maternal milk and blood were reported to be high over the first few postnatal days [75]. Diabetes, however, reduces prolactin release. Still, there is no study examining how prolactin in breast milk changes with gestational diabetes. In order for the maintenance of metabolic balance, prolactin levels must remain within the physiological range. In diabetes while prolactin levels are reduced, there appears a decrease in lactose, fat, and protein. It has been suggested that prolactin taken through maternal milk may contribute to the mental development and ion absorption, as well as the maintenance of water balance in infants. Normal prolactin levels vary between 12.1 and 17 μg/L, while they may rise up to 113 μg/L during pregnancy [79].

Resistin (Adipose Tissue-Specific Secretory Factor)

This protein discovered in 2001 by Steppan et al. [80] consists of 108 amino acids and has a molecular weight of ~12.5 kDa. It is called resistin, because it causes insulin resistance. Among biological tissues, it is secreted mainly by the adipose tissue, immune, and epithelial cells [9]. Amounts of resistin were reported to be elevated in type 1 and type 2 diabetes [81]. Additionally, maternal and cord blood of mothers with GDM have higher resistin levels [82]. Resistin was identified in breast milk in 2008 by Ilcol et al. [83]. The researchers reported that serum and milk resistin levels remained high on post-partum days 1–3 and then started to drop on a time-dependent manner. Resistin levels in maternal milk range from 670 ± 18 to 5800 ± 1100 pg/mL [83]. It is yet uncertain if the origin of resistin in breast milk is blood or mammary tissue or both. Besides, even though resistin is associated with insulin resistance, there is not any study examining the changes in the milk of mothers with GDM. Resistin in maternal milk contributes to growth and development by mediating the regulation of energy metabolism in babies [9]. However, the amount of resistin transferred to the infant via maternal milk should not exceed the physiological doses, as high levels of resistin increases the amount of bad cholesterol (low-density lipoprotein—LDL) and thus, leads to cardiovascular diseases [84]. Consequently, it is essential that the amounts of resistin in the milk of mothers with GDM be determined in the shortest term possible. If mothers with GDM are found to have elevated resistin in their milk, these levels must be normalized to prevent the development of cardiovascular diseases in infants.

Visfatin

Discovered in 1994, visfatin (VIS) contains 491 amino acids and has a molecular weight of 52 kDa. Initially, it was named pre-B cell colony-enhancing factor (PBEF) as it magnified the effect of stem cell factors [85], but in 2002 it was renamed as Nampt as it was also a nicotinamide phosphoribosyltransferase involved in nicotinamide adenine dinucleotide (NAD) synthesis [86]. As for its current name Visfatin, it was given this name in 2005 by Fukuhara et al. [87] who found that it was produced in the visceral adipose tissue. In addition to the visceral fatty tissue, visfatin is synthesized in lymphocytes, monocytes, neutrophils, hepatocytes, skeletal muscle, placenta, pneumocytes, and macrophages. Visfatin has insulin-like effects; that is, it reduces the blood glucose level and increases insulin tolerance. It has been suggested that it may be secreted as a compensatory mechanism against hyperglycemia seen in insulin resistance [88]. Type 2 DM patients with extended hyperglycemia have been reported to have elevated plasma visfatin levels [89]. Similarly, pregnant women with gestational diabetes mellitus were found to have higher mean visfatin levels than the control cases. It was noted that the reason for elevated visfatin levels in pregnant women with GDM might be the excessive visfatin synthesis in the placenta [90]. The presence of visfatin in breast milk was first shown in 2012 by Bienertova-Vasku et al. [91] in the milk of 24 breastfeeding mothers through ELISA method. Although the origin of visfatin in breast milk is not known (mammary glands or plasma), maternal milk was reported to have 100 times more visfatin than blood. Besides, visfatin concentration in milk was found to be directly correlated with preconceptional maternal body mass index (BMI). In other words, as BMI increases, so do visfatin amounts. However, the changes in the visfatin levels of mothers with GDM are not known and remain to be a significant topic of study. It has been suggested that visfatin in maternal milk could protect infants against obesity and metabolic syndrome in their later years, since visfatin with its insulin-like action, as stated above, contributes to the regulation of the glucose metabolism [9].

Recommendations

Breast milk demonstrates that it is a unique watery soup for infants with many vitamins, minerals, fats, and big and small multi-functional peptides. The presence of peptides at physiological rates in breast milk may protect infants against pathological conditions. Therefore, if infant formulae sold in markets are prepared in consideration of the physiological values of peptide molecules discovered in breast milk, many diseases that can develop in later years of children's lives like obesity, cardiovascular diseases, and cancer can be delayed or avoided.

Conclusions

Maternal milk contains many small peptides, medium-size peptides, and large peptides/proteins that are involved in the regulation of infant's metabolism. Although the presence of many large and small peptides has been shown in breast milk and these large and small peptides are known to have a part in the etiology of type 2 diabetes, the changes in their concentrations in the milk of mothers with gestational diabetes have not been studied yet. The increase or decrease in the amount of the peptides/proteins in maternal milk may decide the fate of metabolic events programmed by birth to unfold in a harmonious way and mediate the development of some metabolic diseases in later years of life. Therefore, to protect the babies of mothers with gestational diabetes against metabolic diseases that may develop later, it may be necessary to arrange the peptide/protein content of the milk of these mothers. The presence of peptides can be examined using RIA, ELISA or other probe technologies. If certain peptides will be studied in maternal milk using RIA and ELISA methods, the validity of the method to be used must be tested in relation to the previously published method [92]. Besides, as peptides break down easily, the biological samples to be collected must be kept in containers with protease inhibitors. Over the last two decades, more than 600 peptide molecules have been discovered in biological systems [93, 94]. Recognition of the exact peptide content of maternal milk and identification of the changes in these peptides in relation to gestational diabetes can give the pediatricians and obstetricians an idea about the smooth functioning of the infants' metabolism. In brief, observational and prospective studies indicate that when mothers with gestational diabetes breastfeed their babies; they contribute to the regulation of infants' glucose and lipid metabolism and thus reduce their risk of developing T2DM later in life [75]. The regulation of glucose and lipid metabolisms may be associated with the amounts of peptides/proteins that change with breastfeeding. Therefore, it is essential to elucidate the underlying physiological and biochemical pathways.

References

1. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23:373–8.
2. American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care. 2015;38(Supplement 1): S8–16.
3. Cheung N, Byth K. Population health significance of gestational diabetes. Diabetes Care. 2003;267:2005–9.
4. Negrato CA, Mattar R, Gomes MB. Adverse pregnancy outcomes in women with diabetes. Diabetol Metab Syndr. 2012;4:41.
5. Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. Rev Diabet Med. 2012;29:844–54.
6. Emmett PM, Rogers IS. Properties of human milk and their relationship with maternal nutrition Early Hum Dev. 1997;49(Suppl.):S7–28.
7. Ballard O, Morrow AL. Human milk composition nutrients and bioactive factors. Pediatr Clin North Am. 2013;60:49–74.

8. Aydin S, Kuloglu T, Aydin S. Copeptin, adropin and irisin concentrations in breast milk and plasma of healthy women and those with gestational diabetes mellitus. Peptides. 2013;47:66–70.
9. Aydin S. Peptides in breast milk and their benefits for children. Handbook on dietary and nutritional aspects of human breast milk: Wageningen Academic Publishers, Wageningen, The Netherlands; 2013.
10. Kumar KG, Trevaskis JL, Lam DD, et al. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab. 2008;8:468–81.
11. Aydin S. Three new players in energy regulation: preptin, adropin and irisin. Peptides. 2014;56:94–110.
12. Celik E, Yilmaz E, Celik O, et al. Maternal and fetal adropin levels in gestational diabetes mellitus. J Perinat Med. 2013;41:375–80.
13. O'Dowd BF, Heiber M, Chan A, et al. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. Gene. 1993;136:355–60.
14. Tatemoto K, Hosoya M, Habata Y, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun. 1998;251:471–6.
15. Aydin S, Eren MN, Sahin I, et al. The role of apelins in the physiology of the heart. Protein Pept Lett. 2014;21:2–9.
16. Soriguer F, Garrido-Sanchez L, Garcia-Serrano S, et al. Apelin levels are increased in morbidly obese subjects with type 2 diabetes mellitus. Obes Surg. 2009;19:1574–80.
17. Aydin S. The presence of the peptides apelin, ghrelin and nesfatin-1 in the human breast milk, and the lowering of their levels in patients with gestational diabetes mellitus. Peptides. 2010;31:2236–40.
18. Levy B, Chauvet MT, Chauvet J, et al. Ontogeny of bovine neurohypophysial hormone precursors. II. Foetal copeptin, the third domain of the vasopressin precursor. Int J Pept Protein Res. 1986;27:320–4.
19. Seelig E, Bilz S, Keller U, et al. Concentrations of the stress hormone copeptin increase upon hypoglycaemia in patients with type 1 diabetes dependent of hypoglycaemia awareness. PLoS ONE. 2013;8:e72876.
20. Christ-Crain M, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol. 2016;12:168–76.
21. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402:656–60.
22. Hosoda H, Kojima M, Mizushima T, et al. Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. J Biol Chem. 2003;278:64–70.
23. Aydin S, Aydin S, Ozkan Y, et al. Ghrelin is present in human colostrum, transitional and mature milk. Peptides. 2006;27:878–82.
24. Kierson JA, Dimatteo DM, Locke RG, et al. Ghrelin and cholecystokinin in term and preterm human breast milk. Acta Paediatr. 2006;95:991–5.
25. Aydin S, Geckil H, Karatas F, et al. Milk and blood ghrelin level in diabetics. Nutrition. 2007;23:807–11.
26. Aydin S, Ozkan Y, Erman F, et al. Presence of obestatin in breast milk: relationship among obestatin, ghrelin, and leptin in lactating women. Nutrition. 2008;24:689–93.
27. Krause A, Neitz S, Mägert HJ, et al. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. FEBS Lett. 2000;480:147–50.
28. Cicek D, Dağlı AF, Aydin S, et al. Does hepcidin play a role in the pathogenesis of aphthae in Behçet's disease and recurrent aphthous stomatitis? J Eur Acad Dermatol Venereol. 2014;28:1500–6.
29. Aydin S, Celik O, Gurates B, et al. Concentrations of preptin, salusins and hepcidins in plasma and milk of lactating women with or without gestational diabetes mellitus. Peptides. 2013;49:123–30.
30. Park CH, Valore EV, Waring AJ, et al. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem. 2001;276:7806–10.
31. Miseta A, Nagy J, Nagy T, et al. Hepcidin and its potential clinical utility. Cell Biol Int. 2015;39:1191–202.
32. Derbent AU, Simavli SA, Kaygusuz I, et al. Serum hepcidin is associated with parameters of glucose metabolism in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2013;26:1112–5.
33. Choi SO, Cho YS, Kim HL, et al. ROS mediate the hypoxic repression of the hepcidin gene by inhibiting C/EBPalpha and STAT-3. Biochem Biophys Res Commun. 2007;356:312–7.
34. Brown JC, Mutt V, Dryburgh JR. The further purification of motilin, a gastric motor activity stimulating polypeptide from the mucosa of the small intestine of hogs. Can J Physiol Pharmacol. 1971;49:399–405.
35. Yang MG, Qiu XH, Huang YX. Motilin and gastrin in human milk. Zhonghua Fu Chan Ke Za Zhi. 1994;29:133–4.
36. Chiu YC, Kuo MC, Rayner CK, et al. Decreased gastric motility in type II diabetic patients. Biomed Res Int. 2014;2014:894087.
37. Zhang JV, Ren PG, Avsian-Kretchmer O, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 2005;310:996–9.
38. Cowan E, Burch KJ, Green BD, et al. Obestatin as a key regulator of metabolism and cardiovascular function with emerging therapeutic potential for diabetes. Br J Pharmacol. 2016;173:2165–81.
39. Savino F, Benetti S, Lupica MM, et al. Ghrelin and obestatin in infants, lactating mothers and breast milk. Horm Res Paediatr. 2012;78:297–303.

40. Dale HH. On some physiological actions of ergot. J Physiol. 1906;34:163–206.
41. Magon N, Kalra S. The orgasmic history of oxytocin: Love, lust, and labor. Indian J Endocrinol Metab. 2011;15: S156–61.
42. Takeda S, Kuwabara Y, Mizuno M. Concentrations and origin of oxytocin in breast milk. Endocrinol Jpn. 1986;33:821–6.
43. Stock S, Bremme K, Uvnäs-Moberg K. Is oxytocin involved in the deterioration of glucose tolerance in gestational diabetes? Gynecol Obstet Invest. 1993;36:81–6.
44. Quattrocki E, Friston K. Autism, oxytocin and interoception. Neurosci Biobehav Rev. 2014;47:410–30.
45. Miyata A, Arimura A, Dahl RR, et al. Isolation of a novel 38 residue-hypothalamic polypeptide which stimulates adenylate cyclase inpituitary cells. Biochem Biophys Res Commun. 1989;164:567–74.
46. Lee EH, Seo SR. Neuroprotective roles of pituitary adenylate cyclase-activating polypeptide in neurodegenerative diseases. BMB Rep. 2014;47:369–75.
47. Hewage CM, Venneti KC. Structural aspects of gut peptides with therapeutic potential for type 2 diabetes. ChemMedChem. 2013;8:560–7.
48. Borzsei R, Mark L, Tamas A, et al. Presence of pituitary adenylate cyclase activating polypeptide-38 in human plasma and milk. Eur J Endocrinol. 2009;160:561–5.
49. Buchanan CM, Phillips AR, Cooper GJ. Preptin derived from proinsulin-like growth factor II (proIGF-II) is secreted from pancreatic islet beta-cells and enhances insulin secretion. Biochem J. 2001;360:431–9.
50. Yang G, Li L, Chen W, et al. Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Ann Med. 2009;41:52–6.
51. Aslan M, Celik O, Karsavuran N, et al. Maternal serum and cord blood preptin levels in gestational diabetes mellitus. J Perinatol. 2011;31:350–5.
52. Shichiri M, Ishimaru S, Ota T, et al. Salusins: newly identified bioactive peptides with hemodynamic and mitogenic activities. Nat Med. 2003;9:1166–72.
53. Aydin S, Eren MN, Aydin S. Physiology and Clinical Role of Salusin-α and Salusin-β Peptides in the Cardiovascular System Turkiye Klinikleri J Cardiovasc Sci. 2014;26:33–8.
54. Kimura M, Shindo M, Moriizumi T, et al. Salusin-β, an antimicrobially active peptide against Gram-positive bacteria. Chem Pharm Bull (Tokyo). 2014;62:586–90.
55. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005;26(2):19–39.
56. Rosenfeld L. Insulin: discovery and controversy. Clin Chem. 2002;48:2270–88.
57. Jurdjevic M, Tillman CEC. Noble in June 1921, and his account of the discovery of insulin. Bull Hist Med. 2004;78:864–75.
58. Cevreska S, Kovacev VP, Stankovski M, et al. The presence of immunologically reactive insulin in milk of women, during the first week of lactation and its relation to changes in plasma insulin concentration. God Zb Med Fak Skopje. 1975;21:0–35.
59. Ratzmann KP, Steindel E, Hildebrandt R, et al. Is there a relationship between metabolic control and glucose concentration in breast milk of type 1 (insulin-dependent) diabetic mothers? Exp Clin Endocrinol. 1988;92:32–6.
60. Whitmore TJ, Trengove NJ, Graham DF, et al. Analysis of insulin in human breast milk in mothers with type 1 and type 2 diabetes mellitus. Int J Endocrinol. 2012;2012:296368.
61. Oh-I S, Shimizu H, Satoh T, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature. 2006;443:709–12.
62. Aydin S. Multi-functional peptide hormone NUCB2/nesfatin-1. Endocrine. 2013;44:312–25.
63. Li QC, Wang HY, Chen X, et al. Fasting plasma levels of nesfatin-1 in patients with type 1 and type 2 diabetes mellitus and the nutrient-related fluctuation of nesfatin-1 level in normal humans. Regul Pept. 2010;159:72–7.
64. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481:463–8.
65. Bakal U, Aydin S, Sarac M, et al. Serum, Saliva, and Urine Irisin with and Without Acute Appendicitis and Abdominal Pain. Biochem Insights. 2016;9:11–7.
66. Du XL, Jiang WX. Lower circulating irisin level in patients with diabetes mellitus: a systematic review and meta-analysis. Horm Metab Res. 2016;48(10):644–52.
67. Tekin S, Erden Y, Sandal S, et al. Is Irisin an Anticarcinogenic Peptide? Med-Science. 2015;4:2172–80.
68. Gilbert A, Czarkowska-Paczek B, Deptała A. Physical activity in prevention and treatment of colon cancer. Przegl Lek. 2013;70:969–72.
69. Jedrychowski MP, Wrann CD, Paulo JA, et al. Spiegelman BM Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell Metab. 2015;22:734–40.
70. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425–32.
71. Lin J, Barb CR, Matteri RL, et al. Long form leptin receptor mRNA expression in the brain, pituitary, and other tissues in the pig. Domest Anim Endocrinol. 2000;19:53–61.

72. Pérez-Pérez A, Sánchez-Jiménez F, Maymó J, et al. Role of leptin in female reproduction. Clin Chem Lab Med. 2015;53:15–28.
73. Green ED, Maffei M, Braden VV, et al. The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome 7. Genome Res. 1995;5:5–12.
74. Casabiell X, Piñeiro V, Tomé MA, et al. Presence of leptin in colostrum and/or breast milk from lactating mothers: a potential role in the regulation of neonatal food intake. J Clin Endocrinol Metab. 1997;82:4270–3.
75. Alexe DM, Syridou G, Petridou ET. Determinants of early life leptin levels and later life degenerative outcomes. Clin Med Res. 2006;4:326–35.
76. Friesen H, Guyda H, Hardy J. The biosynthesis of human growth hormone and prolactin. J Clin Endocrinol Metab. 1970;31:611–24.
77. Kiefer KA, Malarkey WB. Size heterogeneity of human prolactin in CSF and serum: experimental conditions that alter gel filtration patterns. J Clin Endocrinol Metabol. 1978;46:119–24.
78. Gala RR, Singhakowinta A, Brennan MJ. Studies on prolactin in human serum, urine and milk. Horm Res. 1975;6:310–20.
79. Beda-Maluga K, Pisarek H, Romanowska I, et al. Ultrafiltration an alternative method to polyethylene glycol precipitation for macroprolactin detection. Arch Med Sci. 2015;11:1001–7.
80. Steppan CM, Brown EJ, Wright CM, et al. A family of tissue-specific resistin-like molecules. Proc Natl Acad Sci USA. 2001;98:502–6.
81. Schäffler A, Büchler C, Müller-Ladner U, et al. Identification of variables influencing resistin serum levels in patients with type 1 and type 2 diabetes mellitus. Horm Metab Res. 2004;36:702–7.
82. Vitoratos N, Dimitrakaki A, Vlahos NF, et al. Maternal and umbilical resistin levels do not correlate with infant birth weight either in normal pregnancies and or in pregnancies complicated with gestational diabetes. J Matern Fetal Neonatal Med. 2010;23:1019–23.
83. Ilcol YO, Hizli ZB, Eroz E. Resistin is present in human breast milk and it correlates with maternal hormonal status and serum level of C-reactive protein. Clin Chem Lab Med. 2008;46:118–24.
84. Joksić J, Sopić M, Spasojević-Kalimanovska V, et al. Higher circulating resistin protein and PBMCs resistin mRNA levels are associated with increased prevalence of small dense LDL particles in coronary artery disease patients. Clin Exp Pharmacol Physiol. 2016;43:22–8.
85. Samal B, Sun Y, Stearns G, et al. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol. 1994;14:1431–7.
86. Rongvaux A, Shea RJ, Mulks MH, et al. Pre-B-cell colony-enhancing factor, whose expression is upregulated in activated lymphocytes, is a nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur J Immunol. 2002;32:3225–34.
87. Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307:426–30.
88. Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. Curr Med Chem. 2008;15:1851–62.
89. Zhang XJ, Wang Z, Li HH, et al. Association between both resistin, visfatin and insulin resistance as well as β cell function in the first-degree relatives of type 2 diabetes mellitus. Zhonghua Liu Xing Bing Xue Za Zhi. 2010;31:1393–6.
90. Liang Z, Wu Y, Xu J, et al. Correlations of serum visfatin and metabolisms of glucose and lipid in women with gestational diabetes mellitus. J Diabetes Investig. 2016;7:247–52.
91. Bienertová-Vašků J, Bienert P, Zlámal F, et al. Visfatin is secreted into the breast milk and is correlated with weight changes of the infant after the birth. Diabetes Res Clin Pract. 2012;96:355–61.
92. Aydin S. A short history, principles, and types of ELISA, and our laboratory experience with peptide/protein analyses using ELISA. Peptides. 2015;72:4–15.
93. Lehr S, Hartwig S, Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin Appl. 2012;6:91–101.
94. Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: Facts and expectations at the beginning of the 21st century. Metabolism. 2015;64:131–45.

Chapter 30
Dietary Advice and Glycaemic Control in Women with Type 1 Diabetes During Preconception Counselling, Pregnancy and Breastfeeding

Lene Ringholm, Björg Ásbjörnsdóttir, Henrik Ullits Andersen, Peter Damm and Elisabeth R. Mathiesen

Key Points

- Careful counselling about appropriate diet and good glycaemic control before, during and after pregnancy is important for the health of mother and child.
- There is an increased risk of severe hypoglycaemia during early pregnancy and breastfeeding.
- It is important to address both strict maternal glycaemic control and appropriate gestational weight gain control in the effort to achieve appropriate foetal growth and improved pregnancy outcome.
- A minimum total daily intake of 175 g of carbohydrate, mainly low glycaemic index carbohydrates, is recommended during pregnancy.
- Breastfeeding may reduce obesity, type 1 diabetes and type 2 diabetes in the offspring.
- The recommended extra dietary allowance for maternal energy intake is set at approximately 330 kg calories per day during breastfeeding. A minimum total daily intake of 210 g of carbohydrate is probably wise.
- Weight retention after the pregnancy should be avoided.
- During breastfeeding insulin requirements are markedly lower than before and during pregnancy.

Keywords Pregnancy · Type 1 diabetes · Preconception counselling · Breastfeeding · Hypoglycaemia · Gestational weight gain · Carbohydrate counting

L. Ringholm (✉) · H.U. Andersen
Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, Gentofte 2820, Denmark
e-mail: enel@dadlnet.dk; lene.ringholm@regionh.dk

H.U. Andersen
e-mail: henrik.ullits.andersen@regionh.dk

B. Ásbjörnsdóttir · E.R. Mathiesen
Center for Pregnant Women with Diabetes, Department of Endocrinology PE7831,
Rigshospitalet University Hospital of Copenhagen, Faculty of Health and Medical Sciences,
University of Copenhagen, Blegdamsvej 9, Copenhagen, Denmark
e-mail: bjoerg.asbjoernsdottir.01@regionh.dk

E.R. Mathiesen
e-mail: elisabeth.reinhardt.mathiesen@regionh.dk

Peter Damm
Center for Pregnant Women with Diabetes, Department of Obstetrics,
Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
e-mail: pdamm@dadlnet.dk

Peter Damm
Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_30

Abbreviations

ADA American Diabetes Association
Kcal Kilogram calories
LGA Large for gestational age
NICE National Institute for Health and Care Excellence
IOM Institute of Medicine

Introduction

Pregnancy in women with type 1 diabetes is associated with an increased risk of adverse outcomes, including congenital malformations, preterm delivery, macrosomia and perinatal death [1]. The risk for these adverse outcomes is 2–4 times higher than in the background population [2]. Unplanned pregnancies with non-optimal glycaemic control contribute to these high rates of maternal and neonatal complications [3]. Although several perinatal outcomes seem to have improved over the last years, the prevalence of macrosomia has increased significantly [4]. Macrosomia is associated with increased neonatal morbidity as well as a long-term increased risk of obesity and metabolic disorders. Moreover, macrosomia can cause major problems during labour, such as emergency caesarean delivery or instrument delivery, shoulder dystocia and laceration of the birth canal.

Pregnant women with type 1 diabetes probably have better glycaemic control now than in the past. Meanwhile there is a strong positive association between excessive gestational weight gain and foetal overgrowth, even after adjustment for HbA1c and pre-pregnancy BMI [5].

These clinical findings highlight the importance of obtaining and maintaining strict glycaemic control before and during pregnancy to optimize maternal and foetal outcomes. In addition, increased clinical focus on appropriate gestational weight gain is important in the effort against neonatal overweight in the infants of women with type 1 diabetes [1, 5].

This textbook chapter highlights factors of importance for the clinical care of women with type 1 diabetes during preconception counselling, pregnancy and breastfeeding with particular focus on dietary advice, glycaemic control and appropriate gestational weight gain.

Preconception Counselling of Women with Type 1 Diabetes

In women with type 1 diabetes, it is important to deliver careful preconception counselling to make a clinical estimation of the risk for maternal and foetal complications during pregnancy. Evaluation of the glycaemic status includes self-monitored glucose values, HbA1c and risk of severe hypoglycaemia [1, 6].

An increasing number of women with type 1 diabetes is overweight and obese. Therefore, during preconception counselling and in early pregnancy, it is important to deliver patient information about limiting gestational weight gain [7].

In general, women with diabetes are recommended to follow the guidelines for healthy women during pregnancy and smoking and alcohol consumption are strongly discouraged during pregnancy [1, 6].

The use of safe contraception in the planning phase is recommended until good glycaemic control assessed by HbA1c level has been established [8, 9].

Glycaemic Control Before and During Pregnancy

Poor glycaemic control before and in early pregnancy is associated with pregnancy complications such as congenital malformations, preterm delivery and preeclampsia [1, 6]. It is therefore an important goal to obtain and maintain strict glycaemic control in the period up to conception with an HbA1c as close to normal as possible, at least <53 mmol/mol (7.0%) [10, 11]. The American Diabetes Association (ADA) recommends glycaemic control as close to normal as is safely possible, ideally HbA1c < 48 mmol/mol (6.5%) to reduce the risk of congenital anomalies [8].

During pregnancy maintenance of strict glycaemic control is of utmost importance. The ADA recommends HbA1c below 42 mmol/mol (6.0%) during pregnancy [8] if this can be achieved without significant hypoglycaemia to minimize the risk of large for gestational age (LGA) infants. The Center for Pregnant Women with Diabetes in Copenhagen recommends HbA1c below 40 mmol/mol (5.8%) after 20 weeks.

The challenge is to achieve a level of blood glucose sufficient to prevent adverse outcomes of pregnancy but avoiding hypoglycaemia. The ADA guidelines suggest the following goals for home glucose measurements: fasting glucose values $\leq$5.3 mmol/l (95 mg/dl), 1-h postprandial values $\leq$7.8 mmol/l (140 mg/dl) and 2-h postprandial values $\leq$6.7 mmol/l (120 mg/dl) [8]. The National Institute for Health and Care Excellence (NICE) guidelines are nearly similar and recommend fasting glucose values <5.3 mmol/l (95 mg/dl), 1 h postprandial values <7.8 mmol/l (140 mg/dl) or 2-h postprandial values <6.4 mmol/l (115 mg/dl), if these are achievable without causing problematic hypoglycaemia [7].

Severe Hypoglycaemia

Severe hypoglycaemia is defined as events with symptoms of hypoglycaemia requiring help from another person to actively administer oral carbohydrate or injection of glucagon or glucose in order to restore the blood glucose level [12] and is the main limiting factor for further optimization of glycaemic control in pregnant women with type 1 diabetes [13]. Risk factors for severe hypoglycaemia during pregnancy include a history with severe hypoglycaemia in the year preceding pregnancy, impaired hypoglycaemia awareness, long duration of diabetes, HbA1c $\leq$48 mmol/mol (6.5%) in early pregnancy, fluctuating plasma glucose values ($\leq$3.9 mmol/l or $\geq$10.0 mmol/l), and excessive use of supplementary insulin injections between meals [14, 15]. Pregnancy-induced nausea and vomiting seem not to be contributing factors [15].

Previously severe hypoglycaemia in women with type 1 diabetes occurred 3–5 times more frequently in early pregnancy than in the period prior to pregnancy [14, 15], whereas in the third trimester the incidence of severe hypoglycaemia was lower than in the year preceding pregnancy [15].

Nonetheless, the risk of severe hypoglycaemia in pregnancy can be reduced by 36% while maintaining good glycaemic control when a multifactorial approach (Fig. 30.1) is applied in the routine care setting [16].

- Education of health-care professionals dealing with diabetes care among women with diabetes of child-bearing age in the importance of avoiding severe hypoglycaemia during pregnancy planning and early pregnancy.
- At inclusion in early pregnancy, women reporting a history of severe hypoglycaemia the year preceding pregnancy and/or self-estimated impaired hypoglycaemia awareness should be identified as high-risk patients. These women should be informed about their extraordinary high risk of severe hypoglycaemia during pregnancy and sought motivated to focus on avoiding severe hypoglycaemia. Extra focus on reducing insulin dose and adjusting diet is needed in these women.
- Insulin analogues and, when indicated, insulin pumps can be used, preferably already from the time of pregnancy planning.
- A reduction of insulin dose by 10-20% at 8-16 gestational weeks is advisable; in particular bedtime dose of long-acting insulin should be reduced.
- Supplementary insulin between meals should be used with caution. A maximum of 4 supplementary extra units of rapid-acting insulin for solitary high glucose values before main meals is recommended. Supplementary insulin outside these timepoints for high glucose values should be discouraged.
- Extra carbohydrate intake is recommended to reduce the risk of nocturnal severe hypoglycaemia, if bedtime plasma glucose level is <6.0 mmol/l.
- A maximum of four episodes of mild hypoglycaemia per week is accepted whereof none are nightly.

Fig. 30.1 Multifactorial approach to reduce the risk of severe hypoglycaemia during pregnancy in women with type 1 diabetes (Adapted from [48]). Copyright 2012 John Wiley and Sons. From: Diabetic Medicine April 2012; 29(5): 558–66. Reprinted with permission from John Wiley and Sons

Gestational Weight Gain

In 2009, the Institute of Medicine (IOM) suggested BMI-appropriate gestational weight gain in healthy women [17] (Table 30.1). For women with diabetes, gestational weight gain within the lower limits of the IOM guidelines has been recommended [18].

More than half of pregnant women with type 1 diabetes gain more weight than recommended in the IOM 2009 guidelines [5]. Excessive gestational weight gain is emerging as an important risk factor for foetal overgrowth both in healthy women and in women with type 1 diabetes [5]. There is a strong positive association between gestational weight gain and offspring birth weight, even after adjustment for the possible impact of maternal glycaemic control assessed by HbA1c in late pregnancy and pre-pregnancy BMI [5] (Table 30.2).

The maternal weight should be monitored at each prenatal visit [18]. The weekly weight gain is higher in late compared with early pregnancy [5]. However, weight change in the first half of pregnancy is an important determinant of foetal growth in women without diabetes [18]. Among women with type 1 diabetes, already in early pregnancy, the weight gain is higher in women ending up with excessive gestational weight gain compared with women with appropriate and insufficient gestational weight gain [5].

Table 30.1 Recommendations on total gestational weight gain according to Institute of Medicine guidelines 2009 for healthy women (Adapted from [17]) and Copenhagen guidelines for women with diabetes, based on pre-pregnancy BMI

Pre-pregnancy BMI (kg/m^2)	Total gestational weight gain according to Institute of Medicine guidelines 2009 (kg) Healthy women	Total gestational weight gain according to Copenhagen guidelines (kg) Women with diabetes
$\leq$ 18.5 underweight	12.5–18.0	10.0–15.0
18.5–24.9 normal weight	11.5–16.0	10.0–15.0
25.0–29.9 overweight	7.0–11.5	5.0–8.0
$\geq$ 30.0 obese	5.0–9.0	0–5.0

Table 30.2 Foetal outcomes in 115 women with type 1 diabetes with insufficient, appropriate and excessive gestational weight gain according to the Institute of Medicine recommendations (Adapted from [5])

	Excessive gestational weight gain (n = 62)	Appropriate gestational weight gain (n = 37)	Insufficient gestational weight gain (n = 16)	p value
Birth weight (grams)	3,681	3,395	3,295	0.02
Large for gestational age infants	29 (47%)	11 (30%)	4 (25%)	0.12

Large for gestational age was defined as birth weight $\geq$ 90th percentile [5]

The birth weight of infants born to women with type 1 diabetes is similar to the healthy background population only in the small group of women with type 1 diabetes and inappropriate gestational weight gain [5] (Fig. 30.2). In contrast, the birth weight is slightly higher than in the healthy background population among infants of women with type 1 diabetes who have an appropriate weight gain according to the IOM 2009 guidelines [5].

Based on observations in healthy obese women [19] and national Danish guidelines for healthy normal weight women, the Copenhagen guidelines on appropriate gestational weight gain in women with diabetes have been developed. Table 30.1 compares the IOM guideline for healthy women and the Copenhagen guidelines for women with diabetes. Pragmatic recommendations on appropriate weekly gestational weight gain for women with diabetes according to the Copenhagen guideline are given in Table 30.3.

Dietary Advice in Pregnancy

Dietary modifications are required during pregnancy to cover the energy cost while avoiding excessive gestational weight gain. The recommended total daily carbohydrate intake is at least 175 g [17]. The overall aim when tailoring a diet for pregnant women with type 1 diabetes is to avoid single large meals and foods with a high content of simple carbohydrates. Carbohydrate counting is useful to match the dose of rapid-acting insulin to the amount of carbohydrate intake at mealtimes and

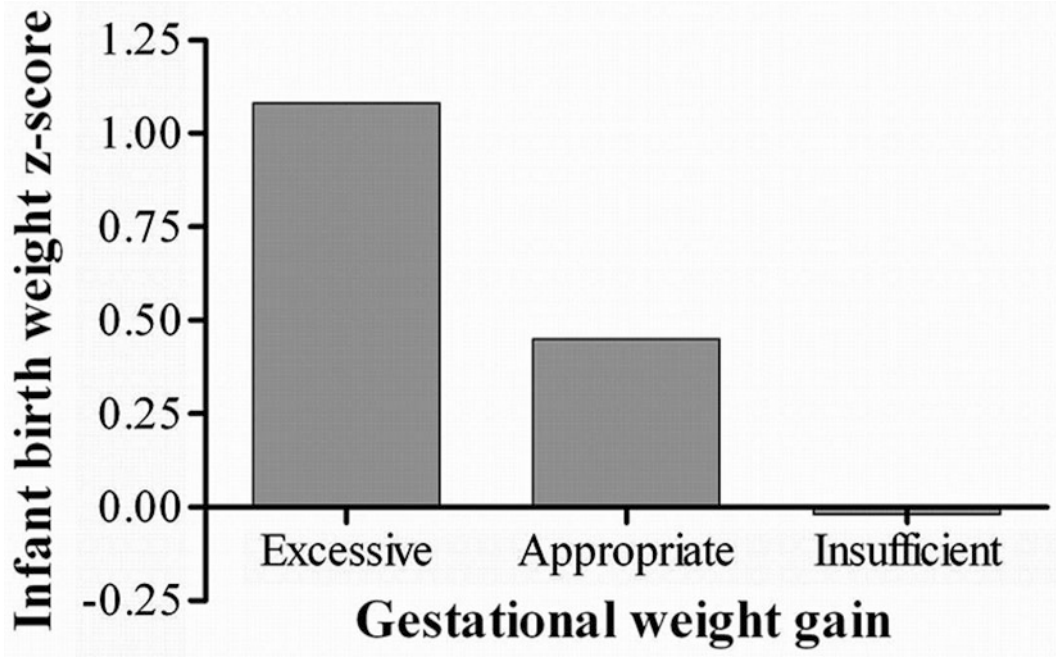


Fig. 30.2 Median infant birth weight SD score in 115 women with type 1 diabetes classified by excessive, appropriate, or insufficient gestational weight gain (Adapted from [5]). The birth weight SD score indicates how far [in standard deviations (SD)] the infant birth weight is from the mean background population after adjustment for gender and gestational age. Mean birth weight SD score in the background population is zero. Copyright 2014 American Diabetes Association. From: Diabetes Care November 2014; 37: 2677–2684. Reprinted with permission from *The American Diabetes Association*

Table 30.3 Recommendations on appropriate weekly weight gain during pregnancy in women with diabetes according to the Copenhagen guidelines

Pre-pregnancy BMI (kg/m^2)	Weekly weight gain until 20 gestational weeks (grams)	Weekly weight gain from 20 gestational weeks until delivery (grams)
≤ 24.9	100	400
25.0–29.9	100	300
≥ 30.0	0	200

occasional review of recorded food intake may also be helpful. The IOM recommends healthy women to obtain 45–65% of total daily calories from carbohydrate [20]. A moderately low carbohydrate diet with 40% carbohydrates has been suggested for pregnant women with type 1 diabetes [21]. A pragmatic and patient friendly way to handle the advice of a minimum total daily intake of 175 g carbohydrate is to recommend intake of 150 g of carbohydrate from the main sources such as bread, fruits, rice, potatoes and pasta leaving 25 g for carbohydrate from vegetables or other carbohydrate sources in the diet [21]. Apps to ease carbohydrate counting are available in many languages.

Recommendations on carbohydrate intake include 20, 40 and 40 g at breakfast, lunch and dinner, respectively, and 10–20 g at snacks. Meticulous timing of meals and snacks is probably of value to prevent both hyperglycaemia and hypoglycaemia in pregnant women with type 1 diabetes [21] (Fig. 30.3).

In order to help women with type 1 diabetes in preventing excessive gestational weight gain, it is currently the practice in our centre to recommend a diet consisting of approximately 175 g of

- Gestational weight gain within the lower limits of the Institute of Medicines guidelines or according to the Copenhagen guidelines for women with diabetes
- Diet mainly containing low glycaemic index carbohydrates
- Carbohydrate counting at each meal and snack
- Moderately low carbohydrate diet of minimum 175 gram per day
- Consistent timing of three meals and 2-4 snacks daily

Fig. 30.3 Dietary advice for pregnant women with type 1 diabetes (Adapted from [21]). The original source of publication: Journal of Maternal Foetal Neonatal Medicine 2015; 28(2):229–33. Reprinted with permission from Taylor & Francis Ltd. http://www.tandfonline.com

carbohydrate per day during pregnancy followed by adjustments according to the weekly weight development.

There are ongoing studies in our centre about the clinical impact of daily carbohydrate counting and intake of mainly low glycaemic index carbohydrates on gestational weight gain, glycaemic control and foetal growth in pregnant women with type 1 diabetes.

Vitamin D

Vitamin D insufficiency, defined as 25-hydroxy vitamin D levels below 50 nmol/l, occurs in up to 80% of pregnancies both among healthy women and women with type 1 diabetes, depending on geographic area, ethnicity and sunlight exposure [22, 23].

Recent evidence among healthy pregnant women supports that low maternal vitamin D status is positively associated with an increased risk of adverse pregnancy outcomes such as preterm birth (<37 gestational weeks) and preeclampsia [24].

The association between vitamin D levels and preeclampsia in type 1 diabetes has only been studied in one longitudinal study. Among 23 women with type 1 diabetes developing preeclampsia, there was a trend towards lower vitamin D levels from 12 gestational weeks compared with 24 women with type 1 diabetes who did not develop preeclampsia. Vitamin D levels were generally lower in the women with type 1 diabetes compared with 24 healthy pregnant women [25].

Supplementation with 10 μg of vitamin D daily is recommended to all pregnant and breastfeeding women in some countries, i.e. the UK [7] and the USA [26].

Interventional studies demonstrate that vitamin D supplementation during pregnancy optimizes maternal and neonatal vitamin D status. Large, well designed, multicenter randomized clinical trials are required to determine whether vitamin D supplementation in pregnant women with low vitamin D status reduces the risk of adverse pregnancy outcomes [24].

Folic Acid

Daily folic acid supplementation during the first 12 gestational weeks is recommended to reduce the incidence of congenital malformations in pregnant women with diabetes and the intake should preferably begin in the pregnancy planning period [27]. There is no consensus on the dose of folic acid and doses ranging from 400 μg/day to 5 mg/day have been recommended [28].

Obstetric Surveillance

In late pregnancy close obstetrical surveillance including frequent ultrasound examinations of foetal growth is important to diagnose foetal overgrowth and to plan the time and mode of delivery with focus on preventing vaginal birth of a macrosomic infant and reducing the prevalence of preterm delivery [1, 6].

Breastfeeding in Women with Type 1 Diabetes

Full breastfeeding for the first 4–6 months of life is recommended by the World Health Organization [29]. Long-term breastfeeding probably prevents future obesity [30, 31] and may protect against development of type 1 diabetes [32] and type 2 diabetes [33] in the offspring.

Aiming at full breastfeeding is of importance for obtaining the full benefit of breastfeeding [30, 34]. Early breastfeeding initiated in the first 30 min of life and repeated 10–12 times per 24 h may reduce the risk of neonatal hypoglycaemia [35]. The rate of full breastfeeding 4 months after delivery among the general population in our area has increased from 50 to 62% during the last decade [36]. However, our study group has shown that this rate has not increased in the same period among women with type 1 diabetes [36] even though offspring of women with type 1 diabetes are now healthier, nursed more frequently immediately after delivery, and maternal smoking is less prevalent than 10 years ago [36, 37].

In women with type 1 diabetes, previous experience with breastfeeding, higher educational level and number of feedings in the first 24 h after delivery are positively associated with longer breastfeeding whereas higher pre-pregnancy BMI and smoking are negatively associated with breastfeeding 4 months after delivery [36–38]. Meanwhile at our centre operative delivery has not been identified as an independent predictor of reduced breastfeeding [36, 37], probably due to similar nursing practices in all newborns of women with diabetes [36, 37, 39].

Glycaemic Control During Breastfeeding

Lactose, one of the major constituents of breast milk, is synthesized from glucose and galactose. Consequently, glucose uptake into mammary tissue for milk production could reduce maternal glucose levels and thus increase the prevalence of hypoglycaemia [40], particularly within 1 hour after breastfeeding [35]. Fluctuating glucose levels during breastfeeding and excessive insulin dose may contribute to an increased risk of severe maternal hypoglycaemia during breastfeeding [1].

In women with type 1 diabetes, immediately after delivery the need for insulin declines to approximately 60% of the pre-pregnancy dose owing to lack of placental hormonal influence. Insulin requirements gradually increase over the next weeks [1]. Four months after delivery, insulin requirement is 21% lower during breastfeeding and 2% higher in bottle formula feeding women with type 1 diabetes mainly treated with multiple daily injections when compared with insulin requirement before pregnancy [36]. HbA1c and occurrence of mild and severe hypoglycaemia has been reported to be similar in women who were breastfeeding and those who were not [36]. In women with type 1 diabetes on insulin pump therapy during breastfeeding, a decrease in the basal insulin requirement within the first 2 months after delivery and an increased risk of hypoglycaemia within 2 weeks after delivery has been reported [41].

A small study of blinded continuous glucose monitoring for up to 6 days in eight breastfeeding and eight bottle formula feeding women with type 1 diabetes 2–4 months after delivery showed similar hypoglycaemia and insulin doses in both groups. In the breastfeeding women, glucose variability was lower and carbohydrate intake tended to be higher compared with the bottle formula feeding women [40].

Dietary Advice During Breastfeeding

The energy requirements are greater in women who breastfeed than in women who do not breastfeed. The extra energy cost of exclusive breastfeeding from birth through 6 months after delivery is approximately 500 kg calories (kcal) per day [42, 43]. Weight loss will subsidize this cost by approximately 170 kcal per day from energy stores accumulated during pregnancy, so the recommended extra dietary allowance for energy during the first 6 months of exclusive breastfeeding is set at 330 kcal per day [35].

To reduce the risk of hypoglycaemia in the postnatal period, especially when breastfeeding, the NICE guidelines recommend that women with type 1 diabetes are advised to have a meal or snack available before or during breastfeeding [7]. Night-time hypoglycaemia may occur due to breastfeeding during the night. If night-time hypoglycaemia is documented, the evening dose of long-acting insulin should be decreased [35]. At our maternity clinic, we routinely recommend an intake of 10–20 g of carbohydrate before or during each breastfeeding, also during night-time, to prevent hypoglycaemia. However, it needs to be explored whether this recommendation is relevant in women with type 1 diabetes who have an appropriate diet and who are on modern insulin treatment.

According to current trend among healthy women, many women with diabetes also follow a diet with low carbohydrate content. However, during breastfeeding women with type 1 diabetes should probably refrain from such a diet because they require a higher carbohydrate intake for milk production than women who do not breastfeed. The extra demand for carbohydrates may contribute to the occurrence of severe hypoglycaemia in these women, especially if the muscular and hepatic carbohydrate stores are insufficient. As in pregnancy, carbohydrate counting and occasional review of recorded food intake may be useful in the breastfeeding period.

During breastfeeding it is probably wise to recommend a total daily intake of minimum 210 g carbohydrate, mainly via low glycaemic index carbohydrates [20]. This should provide enough carbohydrate in the diet for an adequate volume of milk, to prevent ketonaemia and to maintain appropriate blood glucose levels during breastfeeding [44]. Women who are breastfeeding are recommended to consume at least 1800 kcal per day [35].

Weight Loss After Pregnancy

When adequate breastfeeding and maternal nutritional intake are established, it is possible for breastfeeding women to obtain gradual weight loss without harm to the infant [35]. Changes in weight during breastfeeding are variable and depend on amount of gestational weight gain, breastfeeding pattern and duration, physical activity, pre-pregnancy BMI and maternal age [42, 45].

One longitudinal study of 110 healthy women with uneventful pregnancies showed that, regardless of breastfeeding practice, women consistently lost weight from 0.5 to 18 months after delivery, with slower rates of weight loss occurring after 12 months. Overall, less weight was retained by breastfeeding women than by women who were not breastfeeding. Even women who breastfed for less than 4 months retained less weight than bottle formula feeding women. Breastfeeding women achieved their pre-pregnancy weights 6 months earlier than bottle formula feeding women. Importantly, women with greater gestational weight gain had greater weight retention after delivery [45].

In a retrospective follow-up study of more than 5,000 healthy women, weight retention was 1.38 kg less in women who exclusively breastfed for more than 6 months compared with women who did not breastfeed [46]. Meanwhile, a cohort study of more than 4,000 healthy women showed that those who breastfed had less than 1 kg weight change from pre-pregnancy or first trimester to 1–2-year after delivery. The magnitude of weight change was unaffected by breastfeeding versus bottle formula feeding and the duration of breastfeeding [47].

In women with type 1 diabetes weight retention 4 months after delivery was similar in women who were breastfeeding and those who were not [36]. Further studies are warranted to elucidate the effect of weight development after delivery on glycaemic control and well-being in women with type 1 diabetes.

In the meantime, it is important that dietary guidelines for pregnant and breastfeeding women with type 1 diabetes include ways to prevent weight retention after delivery.

Recommendations for Maternal Diet and Glycaemic Control

Preconception counselling

- Women who are planning to become pregnant should be carefully informed that establishing good blood glucose control with HbA1c < 53 mmol/mol (7.0%) before conception will reduce the risk of maternal and foetal complications.
- It is important to use safe contraception in the planning phase.
- Avoid severe hypoglycaemia.
- Supplementation with folic acid from pregnancy planning until 12 gestational weeks.
- Women should be advised on how to limit gestational weight gain.

Pregnancy

- Aim for strict glycaemic control with HbA1c at least below 42 mmol/mol (6.0%).
- Avoid severe hypoglycaemia.
- Supplementation with folic acid during the first 12 gestational weeks.
- Aim for appropriate gestational weight gain.
- The meal plan should include a minimum total daily intake of 175 g carbohydrate, mainly via low glycaemic index carbohydrates.
- Consistent timing of three main meals and 2–4 snacks daily, with carbohydrate counting at each meal and snack.
- Tight obstetric surveillance.

Breastfeeding

- Promotion of breastfeeding has high priority because of its advantages for newborns.
- Immediately after delivery the need for insulin declines to approximately 60% of the pre-pregnancy dose.
- Avoid severe hypoglycaemia.

- Aim for prevention of maternal weight retention 3–6 months after delivery.
- The meal plan should include a minimum total daily intake of 210 g carbohydrate, mainly with low glycaemic index carbohydrates.
- Three main meals and 2–4 snacks daily, with carbohydrate counting at each meal and snack.
- A meal or snack containing at least 10–20 g carbohydrates before or during breastfeeding is recommended to prevent maternal hypoglycaemia.

Conclusions

In women with type 1 diabetes, the goal for glycaemic control during pregnancy is to maintain glucose values within normal ranges and to prevent hypoglycaemia. It is important to obtain appropriate gestational weight gain in the effort to achieve normal foetal growth. During breastfeeding appropriate carbohydrate intake is important in obtaining good glycaemic control without hypoglycaemia. Focus on avoiding weight retention 3–6 months after delivery may contribute to avoidance of maternal overweight and obesity.

References

1. Ringholm L, Mathiesen ER, Kelstrup L, Damm P. Managing type 1 diabetes mellitus in pregnancy–from planning to breastfeeding. Nat Rev Endocrinol. 2012;8(11):659–67.
2. Colstrup M, Mathiesen ER, Damm P, Jensen DM, Ringholm L. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications? J Matern Fetal Neonatal Med. 2013;26(17):1682–6.
3. Lapolla A, Dalfra MG, Di Cianni G, Bonomo M, Parretti E, Mello G, et al. A multicenter Italian study on pregnancy outcome in women with diabetes. Nutr Metab Cardiovasc Dis. 2008;18(4):291–7.
4. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diab Care. 2009;32(11):2005–9.
5. Secher AL, Parellada CB, Ringholm L, Asbjornsdottir B, Damm P, Mathiesen ER. Higher gestational weight gain is associated with increasing offspring birth weight independent of maternal glycemic control in women with type 1 diabetes. Diab Care. 2014;37(10):2677–84.
6. Ringholm L, Damm JA, Vestgaard M, Damm P, Mathiesen ER. Diabetic nephropathy in women with preexisting diabetes: from pregnancy planning to breastfeeding. Curr Diab Rep. 2016;16(2):12.
7. Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. London: National Institute for Health and Care Excellence: Clinical Guidelines; 2015.
8. American Diabetes Association. 13. Management of diabetes in pregnancy. Diab Care. 2017;40 Suppl 1:S114–9.
9. Damm P, Mathiesen E, Clausen TD, Petersen KR. Contraception for women with diabetes mellitus. Metab Syndr Relat Disord. 2005;3(3):244–9.
10. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. Diab Care. 2007;30(7):1920–5.
11. Jensen DM, Korsholm L, Ovesen P, Beck-Nielsen H, Moelsted-Pedersen L, Westergaard JG, et al. Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. Diab Care. 2009;32(6):1046–8.
12. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diab Care. 2013;36(5):1384–95.
13. Rosenn BM, Miodovnik M, Holcberg G, Khoury JC, Siddiqi TA. Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. Obstet Gynecol. 1995;85(3):417–22.
14. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GH. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. Diab Care. 2002;25(3):554–9.
15. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. Diab Care. 2008;31(1):9–14.

16. Ringholm L, Secher AL, Pedersen-Bjergaard U, Thorsteinsson B, Andersen HU, Damm P, et al. The incidence of severe hypoglycaemia in pregnant women with type 1 diabetes mellitus can be reduced with unchanged HbA1c levels and pregnancy outcomes in a routine care setting. Diab Res Clin Pract. 2013;101(2):123–30.
17. Weight gain during pregnancy: reexamining the guidelines (Internet). The National Academies Press. 2009 (cited April 13 2017). Available from: http://www.nap.edu/catalog.php?record_id=12584.
18. Reader DMTA, Gunderson EP. Medical nutrition therapy. In: Kitzmiller J (editor). Managing preexisting diabetes and pregnancy. The American Diabetes Association; 2008. p. 15–89.
19. Vinter CA, Jensen DM, Ovesen P, Beck-Nielsen H, Jorgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. Diab Care. 2011;34(12):2502–7.
20. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients) (Internet). National Academy Press. 2005 (cited April 13 2017). Available from: http://www.nap.edu/read/10490/chapter/1.
21. Roskjaer AB, Andersen JR, Ronneby H, Damm P, Mathiesen ER. Dietary advices on carbohydrate intake for pregnant women with type 1 diabetes. J Matern Fetal Neonatal Med. 2015;28(2):229–33.
22. Bennett SE, McPeake J, McCance DR, Manderson JG, Johnston P, McGalliard R, et al. Maternal vitamin D status in type 1 diabetic pregnancy: impact on neonatal vitamin D status and association with maternal glycaemic control. PLoS ONE. 2013;8(9):e74068.
23. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol. 2010;202(5):429 e1–9.
24. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2013;26(9):889–99.
25. Azar M, Basu A, Jenkins AJ, Nankervis AJ, Hanssen KF, Scholz H, et al. Serum carotenoids and fat-soluble vitamins in women with type 1 diabetes and preeclampsia: a longitudinal study. Diab Care. 2011;34(6):1258–64.
26. Dietary reference intakes for calcium and vitamin D (Internet). National Academies Press. 2011 (cited April 13 2017). Available from: http://www.ncbi.nlm.nih.gov/books/NBK56056/?report=reader.
27. Wilson RD, Davies G, Desilets V, Reid GJ, Summers A, Wyatt P, et al. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Canada (JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC). 2003;25(11):959–73.
28. Capel I, Corcoy R. What dose of folic acid should be used for pregnant diabetic women? Diab Care. 2007;30(7):e63.
29. World Health Organization. Global Strategy for Infant and young child feeding. 2003. (cited April 13 2017) Available from: http://www.who.int/nutrition/publications/infantfeeding/9241562218/en/.
30. Bergmann KE, Bergmann RL, Von Kries R, Bohm O, Richter R, Dudenhausen JW, et al. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. Int J Obes Relat Metab Disord: J Int Assoc Study Obes. 2003;27(2):162–72.
31. Feig DS, Lipscombe LL, Tomlinson G, Blumer I. Breastfeeding predicts the risk of childhood obesity in a multi-ethnic cohort of women with diabetes. J Matern Fetal Neonatal Med. 2011;24(3):511–5.
32. Sadauskaite-Kuehne V, Ludvigsson J, Padaiga Z, Jasinskiene E, Samuelsson U. Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. Diab Metab Res Rev. 2004;20(2):150–7.
33. Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH. Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. Lancet. 1997;350(9072):166–8.
34. Kimpimaki T, Erkkola M, Korhonen S, Kupila A, Virtanen SM, Ilonen J, et al. Short-term exclusive breastfeeding predisposes young children with increased genetic risk of Type I diabetes to progressive beta-cell autoimmunity. Diabetologia. 2001;44(1):63–9.
35. Inturrisi MTA, Block J, Kitzmiller J. Breast-feeding and diabetes. In: Kitzmiller J (editor). Managing preexisting diabetes and pregnancy. The American Diabetes Association. 2008. p. 697–728.
36. Herskin CW, Stage E, Barfred C, Emmersen P, Ladefoged Nichum V, Damm P, et al. Low prevalence of long-term breastfeeding among women with type 2 diabetes. J Matern Fetal Neonatal Med. 2016;29(15):2513–8.
37. Stage E, Norgard H, Damm P, Mathiesen E. Long-term breast-feeding in women with type 1 diabetes. Diab Care. 2006;29(4):771–4.
38. Knudsen A, Pedersen H, Klebe JG. Impact of smoking on the duration of breastfeeding in mothers with insulin-dependent diabetes mellitus. Acta Paediatr. 2001;90(8):926–30.
39. Rowe-Murray HJ, Fisher JR. Baby friendly hospital practices: cesarean section is a persistent barrier to early initiation of breastfeeding. Birth. 2002;29(2):124–31.
40. Achong N, McIntyre HD, Callaway L, Duncan EL. Glycaemic behaviour during breastfeeding in women with type 1 diabetes. Diab Med. 2016;33(7):947–55.
41. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. Endocr Pract (Official J Am Coll Endocrinol Am Assoc Clin Endocrinol). 2009;15(3):187–93.
42. Butte NF, King JC. Energy requirements during pregnancy and lactation. Publ Health Nutr. 2005;8(7A):1010–27.

43. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–41.
44. Reader D, Franz MJ. Lactation, diabetes, and nutrition recommendations. Curr Diab Rep. 2004;4(5):370–6.
45. Janney CA, Zhang D, Sowers M. Lactation and weight retention. Am J Clin Nutr. 1997;66(5):1116–24.
46. Krause KM, Lovelady CA, Peterson BL, Chowdhury N, Ostbye T. Effect of breast-feeding on weight retention at 3 and 6 months postpartum: data from the North Carolina WIC Programme. Publ Health Nutr. 2010;13(12): 2019–26.
47. Sichieri R, Field AE, Rich-Edwards J, Willett WC. Prospective assessment of exclusive breastfeeding in relation to weight change in women. Int J Obesity Relat Metab Disord J Int Assoc Study Obesity. 2003;27(7):815–20.
48. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, Damm P, Mathiesen ER. Hypoglycaemia during pregnancy in women with Type 1 diabetes. Diab Med. 2012;29(5):558–66.

Part IX
Specific Dietary Components and Weight Gain

Chapter 31
Excessive Gestational Weight Gain and Pregnancy Outcomes in Gestational and Pre-gestational Diabetes

Aoife M. Egan and Fidelma P. Dunne

Key Points

- Clear recommendations for gestational weight gain are described in the 2009 Institute of Medicine guidelines.
- Women with diabetes in pregnancy are considered a high-risk group with increased rates of adverse pregnancy outcomes.
- Over 50% of women with diabetes in pregnancy demonstrate excessive gestational weight gain.
- Excessive gestational weight gain is independently associated with adverse pregnancy outcomes in women with diabetes.
- Lifestyle interventions can result in a reduction in gestational weight gain but they have had minimal effect on obstetric outcomes.

Keywords Gestational weight gain · Type 1 diabetes · Type 2 diabetes · Pre-gestational diabetes · Pregnancy · Gestational diabetes

Abbreviations

BMI	Body mass index
IADPSG	International Association of Diabetes and Pregnancy Study Groups
WHO	World Health Organization

Introduction: Weight Gain in Pregnancy

The topic of appropriate weight gain in pregnancy has been hotly debated over the past century with many women inappropriately adhering to the old adage of "eating for two." Gestational weight gain is a unique and complex biological phenomenon that supports the functions of growth and development of the fetus. It is influenced by changes in maternal physiology and metabolism and also by placental metabolism [1]. The 1990 guidelines published by the Institute of Medicine in the United States gave

A.M. Egan (✉) · F.P. Dunne
Department of Medicine, National University of Ireland Galway, Newcastle, Galway, Ireland
e-mail: aoife.egan@hse.ie

F.P. Dunne
e-mail: fidelma.dunne@nuigalway.ie

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_31

a certain amount of direction on what is considered appropriate gestational weight gain, however, they used weight categories from the Metropolitan Life Insurance tables rather than World Health Organization (WHO) body mass index (BMI) categories. In addition, these older guidelines also included a rather broad range of recommended weight gain for obese women [2]. Furthermore since 1990, the profile of the pregnant population has changed dramatically with many women falling into categories deemed 'high-risk' for adverse pregnancy outcomes. The most significant change is the increased prevalence of overweight and obesity. BMI is an index of weight-for-height that is commonly used to classify obesity in adults and is defined as a person weight in kilograms divided by the square of her height in meters squared (kg/m^2). A BMI of greater than or equal to 25 and 30 kg/m^2 defines overweight and obesity, respectively [3]. Using this definition, worldwide obesity has nearly doubled since 1980, and in 2008 the WHO reported that nearly 300 million women were obese [4]. In keeping with these findings, incidence of maternal obesity at the start of pregnancy is increasing and accelerating. In the United States, there is an obesity prevalence of 21% in pre-pregnant females and European studies have identified a prevalence of approximately 19% among pregnant women [5]. In addition, many women are becoming pregnant at an older age and with preexisting chronic conditions such as hypertension or diabetes [1]. Finally, medical professionals in developed countries face the additional challenge of caring for a higher proportion of women from diverse racial/ethnic subgroups.

In 2009, in the face of these changes, the National Research Council and the Institute of Medicine in the United States held a workshop to examine the preexisting guidelines for weight gain in pregnancy. The work of this committee was sponsored by numerous federal agencies and although tailored toward an American population, their final recommendations have been adapted by many organizations worldwide [1]. The guidelines outlined in Table 31.1 are depicted as a range for each category of pre-pregnancy BMI. The broad range for each category highlights the imprecision of the estimates on which the recommendations were based and the fact that good outcomes are achieved within a range of weight gains [1]. Furthermore, it must be noted that many additional factors may need to be considered for an individual women. These guidelines advise less weight gain as the maternal BMI category increases and compared to the 1990 guidelines, are more conservative in the weight gain advised for those in the obese BMI category [1, 2].

The weight gain guidelines as described above were based on multiple observational studies suggesting that women whose weight gain is outside the recommended ranges are at increased risk of adverse maternal and neonatal outcomes. These adverse outcomes include the development of hypertensive disorders of pregnancy [6, 7], increased risk of cesarean delivery [8], increased infant birth weight [9], and postpartum weight retention [8]. The literature is not clear on the association between excessive gestational weight gain and the development of diabetes mellitus. While it may be theorized that excessive weight gain during pregnancy could result in greater fat deposition and negatively influence insulin sensitivity, evidence to support this is weak and studies vary in their conclusions [1]. In relation to longer term consequences of excessive gestational weight gain, Mamun et al. [10] found that greater gestational weight gain is associated with greater offspring BMI into early adulthood and that this may translate into higher systolic blood pressure in offspring. Most recently, a large study in the United States involving children who began life with a normal birth

Table 31.1 Institute of Medicine guidelines for gestational weight gain [1]

Pregestational BMI category	BMI (kg/m^2)	Recommended total weight gain (kg)	Recommended mean weight gain: trimester 2 and 3 (kg/week)
Underweight	<18.5	12.5–18.0	0.51 (0.44–0.58)
Normal weight	18.5–24.9	11.5–16.0	0.42 (0.35–0.50)
Overweight	25.0–29.9	7.0–11.5	0.28 (0.23–0.33)
Obese	≥30.0	5.0–9.0	0.22 (0.17–0.27)

BMI Body mass index

weight found that maternal weight gain appears to imprint for childhood obesity in the first decade. These findings are significant after adjustment for potential confounders including maternal age, parity and pre-pregnancy BMI. Specifically, the authors concluded that the attributable risk (%) for childhood obesity was 16.4% for excessive gestational weight gain [11].

While the described adverse associations with excessive gestational weight gain are based on a significant body of evidence, women with diabetes in pregnancy were excluded from the majority of included studies. Both pre-gestational and gestational diabetes mellitus are high-risk conditions independently associated with a myriad of adverse maternal and neonatal outcomes. Pre-gestational diabetes (including predominantly type 1 and 2 diabetes) is associated with a congenital malformation rate twice that of the background population, a fivefold increased risk of stillbirth and a threefold increased risk of perinatal mortality and cesarean delivery [12–14]. Compared to the background population, women with gestational diabetes mellitus are found to be more likely to have a premature delivery (odds ratio 1.7) and their infants are more likely to be macrosomic (OR1.2), require admission to the neonatal intensive care unit (OR 3.9) or suffer from neonatal hypoglycemia (OR 3.4) [15]. It is evident that women with diabetes need to be examined separately to determine if excessive gestational weight gain confers additional risk independent of their diagnosis of diabetes and if the 2009 Institute of Medicine guidelines are applicable to these populations.

Excessive Gestational Weight Gain and Pre-gestational Diabetes

The Pedersen hypothesis, also known as the hyperglycemia–hyperinsulinemia hypothesis, states that maternal hyperglycemia results in fetal hyperglycemia and resultant hypertrophy of fetal islet tissue with insulin-hypersecretion and greater fetal utilization of glucose [16]. This concept is used to explain the complications that occur in pregnancies affected by pre-gestational diabetes, and therefore strict maternal glycemic control is a cornerstone in the clinical management of these women [17]. However, a growing body of evidence suggests that other substrates such as lipids probably also contribute to fetal overgrowth in pregnancies of women with diabetes [18–20]. This is particularly evident in those women with diabetes who have strict glycemic control during pregnancy but still experience excessive rates of fetal macrosomia [21, 22]. This has stimulated interest in the independent role of excessive maternal weight gain in fuelling fetal overgrowth in the setting of pre-gestational diabetes and a selection of these studies are described below.

In 2011, Yee et al. [23] published the results of a retrospective cohort study of 2310 women with type 2 diabetes enrolled in the California Diabetes and Pregnancy Program. Gestational weight gain was categorized according to 2009 Institute of Medicine guidelines. The included women were either overweight or obese and were predominantly of Latina ethnicity. Almost 40% of participants gained weight in excess of the guidelines. The authors found that with excessive gestational weight gain, there were increased odds of having large for gestational age (adjusted odds ratio 2.0) or macrosomic (aOR 2.59) neonates and cesarean delivery (aOR 1.47). Women with excessive gestational weight gain had increased odds of preterm delivery (aOR 1.57). A 2014 Danish study also examined the association between gestational weight gain and fetal growth. This retrospective cohort study included 142 pregnancies in women with type 2 diabetes and varying BMI. Excessive gestational weight gain was observed in 43% and their offspring had a higher birthweight (3712 vs. 3258 g) and prevalence of large for gestational age (48 vs. 20%) [24].

Secher et al. [17] subsequently evaluated the association between gestational weight gain and offspring birth weight in singleton term pregnancies of women with type 1 diabetes. This study also based in Denmark examined 115 women and again characterized gestational weight gain according to Institute of Medicine recommendations for each BMI class. In order to reduce confounding, women with nephropathy, preeclampsia and/or preterm delivery were excluded because of restrictive impact

on fetal growth and limited time for total weight gain. Despite comparable HbA1c levels in the first and third trimesters of pregnancy, similar duration of diabetes and median pre-pregnancy BMI, offspring of women with excessive gestational weight gain had higher birth weights compared to those women with appropriate or insufficient weight gain. The authors completed a multiple linear regression analysis and found that gestational weight gain was positively associated with offspring birth weight and birth weight standard deviation score when adjusting for multiple potential confounding factors including pre-pregnancy BMI, HbA1c at 36 weeks, smoking, parity and ethnicity.

In 2014, Egan et al. evaluated a cohort of 802 women with diabetes in pregnancy, of which 259 (32%) had pre-gestational diabetes. The latter group comprised 169 (65%) with type 1 and 90 (35%) with type 2 diabetes. Excessive gestational weight gain was noted in 64% of those with pre-gestational diabetes. Despite adjustments for age, parity, ethnicity, use of insulin, booking BMI category and cigarette smoking, excessive gestational weight gain was associated with higher odds for macrosomia (aOR 3.58) and large for gestational age (aOR 3.97). Finally, Siegel et al. evaluated 340 subjects with pre-gestational diabetes and found that the incidence of large for gestational age and macrosomia increased with gestational weight gain and this was not explained by differences in glycemic control between groups [25].

While these studies are all limited by their retrospective nature, they do demonstrate the independent association of excessive gestational weight gain with adverse pregnancy outcomes in women with pre-gestational diabetes. The association is particularly strong in relation to fetal birth weight. These studies support the use of the 2009 Institute of Medicine guidelines in this high-risk population.

Excessive Gestational Weight Gain and Gestational Diabetes

Gestational diabetes mellitus is defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy [26]. This diagnosis excludes those with diabetes in pregnancy that is likely to represent overt diabetes mellitus. Accurate prevalence estimates of gestational diabetes are lacking and this is in part due to inconsistent screening and diagnostic criteria [27]. In certain European populations however, gestational diabetes is reported in up to 20% pregnancies [28, 29]. The 2008 International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended a diagnosis of diabetes according to the following criteria: fasting plasma glucose ≥ 5.1 mmol/L; 1 h plasma glucose ≥ 10.0 mmol/L or 2 h plasma glucose ≥ 8.5 mmol/L [30]. These recommendations based on the results of the Hyperglycemia and Neonatal Outcomes (HAPO) study [31] have been endorsed by the World Health Organization [26], the Endocrine Society in the United States [32] and the International Federation of Gynecology and Obstetrics (FIGO) [33]. The National Institute for Health and Care Excellence in the United Kingdom have adapted a different approach and recommended that gestational diabetes is diagnosed if the woman has either a fasting plasma glucose of ≥ 5.6 mmol/L or a 2 h plasma glucose level of ≥ 7.8 mmol/L [14]. Notwithstanding the variations in diagnosis, women with gestational diabetes are at risk of adverse pregnancy outcomes compared to the background population. In addition, maternal overweight and obesity frequently coexist in these women, both of which are associated with elevated risk of adverse pregnancy outcomes including hypertension, preterm birth, cesarean delivery, and infant macrosomia [34, 35]. To date, a significant number of studies have sought to determine the independent effects of excessive gestational weight gain in pregnancies complicated by gestational diabetes.

In 2011, a study based in California examined 1502 women of varying BMI and a diagnosis of gestational diabetes. They found that women who exceeded the Institute of Medicine guidelines for gestational weight gain were 3 times more likely to have a macrosomic infant [36]. Subsequently in 2013, Black et al. published a retrospective study including 9835 women with and without gestational

diabetes and mainly of Hispanic ethnicity. These women were untreated with diet, exercise or anti-diabetic medications during pregnancy. The results demonstrated a higher incidence of large for gestational age infants in the presence of gestational weight gain in excess of Institute of Medicine recommendations [37]. The Atlantic-Diabetes in Pregnancy research group, located along the Irish Atlantic seaboard examined 543 women with gestational diabetes diagnosed and treated according to IADPSG criteria [38]. Mean weight gain per week throughout the second and third trimester of pregnancy was calculated and compared with Institute of Medicine guidelines to assess whether the upper recommended limit as per BMI category was breached. The authors found that 57% of the cohort had excessive gestational weight gain and this was more frequent among women with an overweight BMI at booking. After correcting for confounding factors, women who demonstrated excessive gestational weight gain had higher odds for large for gestational age birth weight (aOR 2.01), macrosomia (aOR 2.17), and gestational hypertension (aOR 1.72). Interestingly, it was also found that the effects of excessive gestational weight gain were further compounded by an additive effect of insulin therapy. This observation requires scientific studies of mechanism to further investigate but does suggest that insulin may not be the most appropriate first-line therapy for management of gestational diabetes. Using a different approach with linked birth certificate and maternal hospital discharge data of live, singleton deliveries in Florida, Kim et al. used multivariable logistic regression to assess the independent contributions of maternal BMI, gestational weight gain and gestational diabetes status on large for gestational age risk [39]. The authors concluded that for all race or ethnic groups, gestational diabetes contributed the least (2.0–8.0%) and excessive weight gain contributed the most (33.3–37.7%) to large for gestational age.

These findings are supported by a number of more recent studies. Gante et al. [40] evaluated 1806 Portuguese, obese women with gestational diabetes who delivered between 2008 and 2012 [40]. In this study, women were diagnosed with gestational diabetes based on either IADPSG criteria or the older Carpenter and Coustan's criteria [41]. Again the authors found a high rate of excessive gestational weight gain at 37.1%. After adjusting for birth weight, excessive weight gain was associated with higher odds for cesarean delivery (aOR 1.31), low Apgar score at birth (aOR 4.79), large for gestational age neonates (aOR 2.32), and macrosomia (aOR 2.39). Finally, Harper et al. [42] sought to assess the impact of gestational weight gain outside the Institute of Medicine recommendations after the diagnosis of gestational diabetes on perinatal outcomes [42]. Of 635 included women, 58% gained excessive weight and the authors demonstrated that the risk of cesarean delivery and the need for pharmacological treatment of the diabetes increased in those gaining above the recommendations. They further revealed that for every 1-lb per week increase in weight gain after diagnosis of gestational diabetes, there was a 36–83% increase in the risk of complications such as preeclampsia, cesarean delivery, need for pharmacological treatment of diabetes, infant macrosomia, and large for gestational age.

Similar to women with pre-gestational diabetes, this ever-growing body of evidence in women with gestational diabetes suggests that excessive weight gain is common and independently associated with an increased risk of adverse pregnancy outcomes in this population.

Recommendations: Ways to Prevent Excessive Gestational Weight Gain

As discussed, pregnant women are heavier than at any time in the past [1]. Furthermore, approximately 50% of pregnancies are unplanned and women with diabetes already face the unique challenges associated with managing this condition [43, 44]. In addition, in a significant number of cases, dietary trends have seen a move away from energy dense foods toward solid fats, alcoholic beverages, and added sugars [1]. Finally, data shows that one in five women aged 18–29 years and almost

a quarter of those in their 30s and 40s reported no physical activity [45]. In light of these facts, it is easy to see that preventing excessive gestational weight gain may present a significant challenge.

The first step toward ensuring women gain weight within the recommended guidelines is letting them know that they exist. In this regard, healthcare professionals caring for pregnant women should provide this education and develop individualized weight gain goals with regular monitoring and discussion of weight gain throughout the pregnancy. The Institute of Medicine has included useful weight gain charts in their 2009 report that are meant to be used as part of the assessment of the progress of pregnancy and will help illustrate the pattern of the woman's weight gain [1]. Selected women may need additional assistance to achieve their goal. For example, Carmichael et al. have recommended that women should be evaluated for factors that may be leading to abnormal gestational weight gain such as lack of money, stress, presence of infection, or other medical problems [46]. Physical activity clearly plays a role in achieving weight gain targets. The American College of Obstetricians and Gynecologists (ACOG) advise that physical activity in pregnancy has minimal risks and has been shown to benefit most women, although some modification to exercise routines may be necessary because of normal anatomic and physiologic changes and fetal requirements [47]. After a clinical evaluation, women with uncomplicated pregnancies should be encouraged to engage in 150 min per week of moderate-intensity aerobic and strength-conditioning exercises. In general, there is no specific contraindication to exercise in the setting of diabetes, although women on glucose lowering medication require education on the risk of hypoglycemia. In addition, those women receiving insulin therapy may need to dose adjust their insulin depending on the intensity and duration of exercise. This must be considered on a case-by-case basis. Exercise has shown a modest decrease in overall weight gain (1–2 kg) in normal weight, overweight, and obese women [48, 49]. It must be noted that certain activities including contact sports, scuba diving, sky diving, hot yoga, and activities with a high-risk of falling are not recommended in pregnancy [47]. The Royal College of Obstetricians and Gynecologists in the United Kingdom echo the recommendations of the ACOG and advise that in most cases exercise is safe for both mother and fetus during pregnancy [50]. In addition to exercise advice, dietary changes are typically necessary to ensure appropriate gestational weight gain. All women with pre-gestational diabetes require dietetic support during their pregnancy and dietary changes form the cornerstone of the initial approach to management of gestational diabetes [44, 51]. Ideally, this support will come from a dietician specializing in pregnancy. Women with diabetes should be encouraged to eat a healthy diet during pregnancy and there should be a particular focus on replacing foods with a high glycemic index with low-glycemic index foods in the case of gestational diabetes [14]. In general, sugars and simple carbohydrates should be eliminated with ideal carbohydrate sources including fresh vegetables, some fruits, and whole grains [52]. While theoretically the connection between diet and weight gain is obvious, there is no definitive evidence for the optimal proportion of carbohydrate in the diet of women with diabetes and more research is needed into the relationship between maternal dietary intake and gestational weight gain [32].

Are Weight Gain Interventions Successful?

With a wealth of information on healthy lifestyle approaches, it would be expected that targeted interventions could successfully limit gestational weight gain and improve pregnancy outcomes.

The low-glycemic index diet in pregnancy to prevent macrosomia (ROLO study) randomized controlled trial recruited 800 women without diabetes who previously delivered an infant weighing >4 kg. They were allocated to receive no dietary intervention or start on a low-glycemic index diet from early pregnancy. The primary outcome measure was difference in birth weight and no significant difference was observed between groups. Difference in gestational weight gain was a secondary

outcome and less weight gain did occur in the intervention arm (mean difference 1.3 kg). There was also a lower rate of glucose intolerance in the intervention arm (21% vs. 28%) [53].

Oostdam and colleagues [54] evaluated the effect of an exercise program commencing in the second trimester for pregnant women who were overweight or obese and at risk for gestational diabetes. They randomized 121 women to either a control group or the intervention group. They found no differences in gestational weight gain between the two groups. Additionally there was no effect on maternal fasting glucose levels, insulin sensitivity, or neonatal birth weight. The authors drew attention to the low compliance rates and suggested that future interventions should commence before pregnancy or in early pregnancy. In Finland, a secondary analysis of a cluster-randomized controlled trial examined whether a lifestyle intervention involving counseling on gestational weight gain, physical activity, and healthy eating was effective in reducing excessive gestational weight gain [55]. Although this approach contains all the key elements required to ensure normal gestational weight gain, there was no difference between intervention and usual care groups in terms of mean gestational weight gain. In fact, 46.8% of the intervention group and 54.4% of the usual care group exceeded the weight gain recommendations.

A 2012 systematic review and meta-analysis including 44 randomized controlled trials sought to evaluate the effects of dietary and lifestyle interventions in pregnancy on maternal and fetal weight and to quantify the effects of these interventions on obstetric outcomes [56]. Overall there was a 1.42 kg reduction in gestational weight gain with any intervention compared with control. There were no significant differences in birth weight or incidence of large or small for gestational age infants between control and intervention groups. Interventions were associated with a reduced risk of preeclampsia and shoulder dystocia but disappointingly, no significant effect on other important outcomes. A separate systematic review and meta-analysis evaluated lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcomes [57]. Again there was evidence of a reduction in maternal pregnancy weight gain (mean −2.21 kg) in the intervention groups but no clear differences in terms of other outcomes.

More recently in 2014, the LIMIT randomized trial randomized 2212 overweight or obese women to either standard antenatal care or a comprehensive dietary and lifestyle intervention [58]. The intervention did not reduce the risk of large for gestational age infants or have any effect on gestational weight gain or pregnancy outcomes. Poor compliance with the intervention was cited as a possible cause for the negative outcome. The 2015 UPBEAT study randomized 1555 women to either standard antenatal care or a behavioral intervention addressing diet and physical activity [59]. The aim was to assess if the intervention could reduce the incidence of gestational diabetes or large for gestational age infants. Despite a reduction in gestational weight gain (1.5 kg) in the intervention group, primary outcomes did not differ between groups.

We are awaiting with interest the results of a randomized trial of physical activity and/or healthy eating to reduce the risk of gestational diabetes mellitus also termed the DALI study. The DALI lifestyle pilot however is completed and included 150 participants who were pregnant and at risk for gestational diabetes with a BMI of ≥ 29 kg/m^2 [60]. Participants were randomized to healthy eating, physical activity, or healthy eating and physical activity. Primary outcomes included gestational weight gain, fasting glucose, and insulin sensitivity at 35–37 weeks. Women received a combination of face-to-face and telephone coaching sessions and a gestational weight gain of <5 kg was targeted. Just 20% women achieved the target weight gain and 32% developed gestational diabetes during the pregnancy. The results revealed that those randomized to healthy eating had less gestational weight gain (−2.6 kg) and lower fasting glucose (−0.3 mmol/L) than those in the physical activity groups. No significant differences in insulin sensitivity between groups or between the healthy eating and physical activity group and the other groups were observed.

In relation to pregnancies affected by diabetes, a 2013 Danish retrospective cohort study examined 58 pregnancies in obese women with type 2 diabetes. These women were advised by their healthcare professional to gain 0–5 kg during their pregnancy. The authors sought to examine associations between

fetal growth and gestational weight gain and the safety of advising this weight gain target. For purposes of analysis, they divided the women into those who gained ≤ 5.0 kg ($n = 17$; 29%) and those who gained >5.0 kg ($n = 41$; 71%). In the setting of similar glycemic control, infants of those who gained ≤ 5.0 kg had a lower birth weight z score, lower rates of large for gestational age, delivery closer to term and less perinatal morbidity. Although this was not a randomized controlled trial, the weight gain advise seemed to be safe but was not achieved by the majority of participants [61].

While the selection of studies described provide insights on the effects of attempts of restricted gestational weight gain, the vast majority do not specifically examine women with diabetes, either pre-gestational, or gestational. Overall however, results suggest that lifestyle interventions may have a moderate effect on gestational weight gain but there is no evidence of any major impact on obstetric outcomes as a result.

Areas for Further Research

There are significant knowledge gaps in the area of gestational weight gain in women with diabetes that warrant further research. While certain lifestyle interventions have detected differences in gestational weight gain between groups, many have been inadequately powered to detect differences in obstetric outcomes. Furthermore, the poor compliance rates suggest that many of the study interventions are not acceptable to the population under study. We believe a trial demonstrating that a particular lifestyle intervention can impact on gestational weight gain and also result in superior obstetric outcomes would be extremely useful to clinicians and patients worldwide. Such a study would ideally contain groups of women with diabetes in pregnancy to clarify a benefit in the setting of this coexistent diagnosis.

Conclusions

In women with diabetes in pregnancy, gestational weight gain in excess of 2009 Institute of Medicine recommendations is common and associated with an increased risk of poor obstetric outcomes, particularly in relation to fetal growth [1]. While a number of lifestyle interventions have resulted in a reduction in gestational weight gain, evidence to support an associated improvement in obstetric outcomes does not exist. Furthermore, these studies are not specific to women with diabetes in pregnancy. Until further evidence is available, we advise education of all women regarding their specific weight gain goals according to Institute of Medicine guidelines (Table 31.1). Weight gain should be charted on a regular basis throughout pregnancy and additional support should be provided if targets are not achieved. It is hoped that future research will identify specific interventions to improve outcomes for this high-risk population.

References

1. Instutute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. In: Rasmussen KM, Yaktine AL, editors. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: Naitonal Acadamies Press (US); 2009.
2. Institute of Medicine (US) Committee on Nutritional Status During Pregnancy and Lactation. Nutrition during pregnancy: Part I, weight gain; Part II, nutrient supplements. Washington, DC: National Academy Press (US); 1990.

3. Egan AM, Dennedy MC. Obesity and gestational outcomes. In: Handbook of fertility: nutrition, diet, lifestyle and reproductive health. Watson, RR, editor. Elsevier; 2015.
4. World Health Organisation. Fact Sheet No 311: obesity and overweight; 2014. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.
5. Huda SS, Brodie LE, Sattar N. Obesity in pregnancy: prevalence and metabolic consequences. Semin Fetal Neonatal Med. 2010;15(2):70–6.
6. Thorsdottir I, Torfadottir JE, Birgisdottir BE, Geirsson RT. Weight gain in women of normal weight before pregnancy: complications in pregnancy or delivery and birth outcome. Obstet Gynecol. 2002;99(5 Pt 1):799–806.
7. DeVader SR, Neeley HL, Myles TD, Leet TL. Evaluation of gestational weight gain guidelines for women with normal prepregnancy body mass index. Obstet Gynecol. 2007;110(4):745–51.
8. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, Thieda P, Lux LJ, Lohr KN. Outcomes of maternal weight gain, Evidence Report/Technology Assessment No. 168. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under contract no. 290–02-0016.). AHRQ Publication No. 08-E-09. Rockville, MD: Agency for Healthcare Research and Quality.
9. Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, et al. A systematic review of outcomes of maternal weight gain according to the institute of medicine recommendations: birthweight, fetal growth, and postpartum weight retention. Am J Obstet Gynecol. 2009;201(4):339.e1–14.
10. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. Circulation. 2009;119(13):1720–7.
11. Hillier TA, Pedula KL, Vesco KK, Oshiro CE, Ogasawara KK. Impact of maternal glucose and gestational weight gain on child obesity over the first decade of life in normal birth weight infants. Matern Child Health J. 2016;[Epub ahead of print].
12. Dunne FP, Avalos G, Durkan M, Mitchell Y, Gallacher T, Keenan M, et al. ATLANTIC DIP: pregnancy outcome for women with pregestational diabetes along the Irish Atlantic seaboard. Diabetes Care. 2009;32(7):1205–6.
13. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006;333(7560):177.
14. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. London; 2015. Available from https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-from-preconception-to-the-postnatal-period-51038446021.
15. O'Sullivan EP, Avalos G, O'Reilly M, Dennedy MC, Gaffney G, Dunne F, et al. Atlantic diabetes in pregnancy (DIP): the prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. Diabetologia. 2011;54(7):1670–5.
16. Pedersen J. The pregnant diabetic and her newborn: problems and management. Baltimore MD: William & Wilkins; 1967. p. 128–37.
17. Secher AL, Parellada CB, Ringholm L, Asbjörnsdóttir B, Damm P, Mathiesen ER. Higher gestational weight gain is associated with increasing offspring birth weight independent of maternal glycemic control in women with type 1 diabetes. Diab Care. 2014;37(10):2677–84.
18. Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol. 2011;204(6):479–87.
19. Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diab Care. 2008;31(9):1858–63.
20. Kulkarni SR, Kumaran K, Rao SR, Chougule SD, Deokar TM, Bhalerao AJ, et al. Maternal lipids are as important as glucose for fetal growth: findings from the Pune maternal nutrition study. Diab Care. 2013;36(9):2706–13.
21. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diab Care. 2013;36(7):1877–83.
22. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia. 2002;45(11):1484–9.
23. Yee LM, Cheng YW, Inturrisi M, Caughey AB. Effect of gestational weight gain on perinatal outcomes in women with type 2 diabetes mellitus using the 2009 Institute of Medicine guidelines. Am J Obstet Gynecol. 2011;205(3):257.e1–6.
24. Parellada CB, Asbjörnsdóttir B, Ringholm L, Damm P, Mathiesen ER. Fetal growth in relation to gestational weight gain in women with type 2 diabetes: an observational study. Diabet Med. 2014;31(12):1681–9.
25. Siegel AM, Tita A, Biggio JR, Harper LM. Evaluating gestational weight gain recommendations in pregestational diabetes. Am J Obstet Gynecol. 2015;213(4):563.e1–5.
26. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization guideline. Diabetes Res Clin Pract. 2014;103(3):341–63.

27. Benhalima K, Mathieu C, Damm P, Van Assche A, Devlieger R, Desoye G, et al. A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). Diabetologia. 2015;58(7):1422–9.
28. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med. 2012;29(7):844–54.
29. Jelsma JG, van Poppel MN, Galjaard S, Desoye G, Corcoy R, Devlieger R, et al. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial—study protocol. BMC Pregnancy Childbirth. 2013;13:142.
30. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care. 2010;33(3):676–82.
31. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.
32. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(11):4227–49.
33. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The international federation of gynecology and obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet. 2015;131(Suppl 3):S173–211.
34. Dennedy MC, Avalos G, O'Reilly MW, O'Sullivan EP, Gaffney G, Dunne F. ATLANTIC-DIP: raised maternal body mass index (BMI) adversely affects maternal and fetal outcomes in glucose-tolerant women according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. J Clin Endocrinol Metab. 2012;97(4):E608–12.
35. Dodd JM, Grivell RM, Nguyen AM, Chan A, Robinson JS. Maternal and perinatal health outcomes by body mass index category. Aust N Z J Obstet Gynaecol. 2011;51(2):136–40.
36. Ouzounian JG, Hernandez GD, Korst LM, Montoro MM, Battista LR, Walden CL, et al. Pre-pregnancy weight and excess weight gain are risk factors for macrosomia in women with gestational diabetes. J Perinatol. 2011;31 (11):717–21.
37. Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diab Care. 2013;36(1):56–62.
38. Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. J Clin Endocrinol Metab. 2014;99(1):212–9.
39. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. Obstet Gynecol. 2014;123 (4):737–44.
40. Gante I, Amaral N, Dores J, Almeida MC. Impact of gestational weight gain on obstetric and neonatal outcomes in obese diabetic women. BMC Pregnancy Childbirth. 2015;15:249.
41. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144 (7):768–73.
42. Harper LM, Tita A, Biggio JR. The institute of medicine guidelines for gestational weight gain after a diagnosis of gestational diabetes and pregnancy outcomes. Am J Perinatol. 2015;32(3):239–46.
43. Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, et al. The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third national survey of sexual attitudes and lifestyles (Natsal-3). Lancet. 2013;382(9907):1807–16.
44. Egan AM, Murphy HR, Dunne FP. The management of type 1 and type 2 diabetes in pregnancy. QJM. 2015;108 (12):923–7.
45. CDC. Trends in leisure-time physical inactivity by age, sex and race/ethnicity—United States, 1994–2004. Morbidity and Mortality Weekly Report; 2005. p. 991–4.
46. Carmichael S, Abrams B, Selvin S. The pattern of maternal weight gain in women with good pregnancy outcomes. Am J Public Health. 1997;87(12):1984–8.
47. The American College of Obstetricians and Gynecologists. Committee opinion number 650: physical activity and exercise during pregnancy and the postpartum period; 2015. Available from https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co650.pdf?dmc=1&ts=20160503T1603497350.
48. Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. Cochrane Database Syst Rev. 2015;6:CD007145.
49. Choi J, Fukuoka Y, Lee JH. The effects of physical activity and physical activity plus diet interventions on body weight in overweight or obese women who are pregnant or in postpartum: a systematic review and meta-analysis of randomized controlled trials. Prev Med. 2013;56(6):351–64.

50. Royal College of Obstetricians and Gynaecologists. Statement no. 4. Exercise in pregnancy; 2006. Available from https://www.rcog.org.uk/globalassets/documents/guidelines/statements/statement-no-4.pdf.
51. Kgosidialwa O, Egan AM, Carmody L, Kirwan B, Gunning P, Dunne FP. Treatment with diet and exercise for women with gestational diabetes mellitus diagnosed using IADPSG criteria. J Clin Endocrinol Metab. 2015;100 (12):4629–36.
52. Castorino K, Jovanovič L. Pregnancy and diabetes management: advances and controversies. Clin Chem. 2011;57 (2):221–30.
53. Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. BMJ. 2012;345:e5605.
54. Oostdam N, van Poppel MN, Wouters MG, Eekhoff EM, Bekedam DJ, Kuchenbecker WK, et al. No effect of the FitFor2 exercise programme on blood glucose, insulin sensitivity, and birthweight in pregnant women who were overweight and at risk for gestational diabetes: results of a randomised controlled trial. BJOG. 2012;119(9):1098–107.
55. Kinnunen TI, Raitanen J, Aittasalo M, Luoto R. Preventing excessive gestational weight gain–a secondary analysis of a cluster-randomised controlled trial. Eur J Clin Nutr. 2012;66(12):1344–50.
56. Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ. 2012;344:e2088.
57. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Med. 2012;10:47.
58. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. BMJ. 2014;348:g1285.
59. Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, et al. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. Lancet Diab Endocrinol. 2015;3 (10):767–77.
60. Simmons D, Jelsma JG, Galjaard S, Devlieger R, van Assche A, Jans G, et al. Results from a European multicenter randomized trial of physical activity and/or healthy eating to reduce the risk of gestational diabetes mellitus: the DALI lifestyle pilot. Diab Care. 2015;38(9):1650–6.
61. Asbjörnsdóttir B, Rasmussen SS, Kelstrup L, Damm P, Mathiesen ER. Impact of restricted maternal weight gain on fetal growth and perinatal morbidity in obese women with type 2 diabetes. Diab Care. 2013;36(5):1102–6.

Chapter 32
Diet and Carbohydrate Food Knowledge in Gestational Diabetes: Challenges and Opportunities for Lifestyle Interventions

Habiba I. Ali, Emilia Papakonstantinou and Najoua El Mesmoudi

Key Points

- Medical nutrition therapy (MNT) is the cornerstone for the management of GDM.
- Dietary components may have both negative and protective effects on the risk for GDM.
- Carbohydrate (CHO) is the primary nutrient affecting postprandial blood glucose levels.
- Women with GDM may have limited nutrition knowledge especially about CHO-containing foods.
- Use of behavior change theories in GDM management has the potential to facilitate changes in dietary behaviors.

Keywords Gestational diabetes mellitus · Dietary behaviors and GDM · Carbohydrate food knowledge · Behavior change theories · Lifestyle changes

Abbreviations

AHEI	Alternate healthy eating index
aMED	Alternate mediterranean diet
AND	The Academy of Nutrition and Dietetics
BMI	Body mass index
CBT	Cognitive behavioral theory
CHO	Carbohydrate
DASH	Dietary approaches to stop hypertension
DRIs	Dietary reference intakes
GDM	Gestational diabetes mellitus
GI	Glycemic index
GL	Glycemic load
MI	Motivational interviewing

H.I. Ali (✉) · N.E. Mesmoudi
Nutrition and Health Department, College of Food and Agriculture,
United Arab Emirates University, P.O. Box 15551, Al Ain, United Arab Emirates
e-mail: habAli@uaeu.ac.ae; habiba.ali9@gmail.com

N.E. Mesmoudi
e-mail: najouam@uaeu.ac.ae; najoomes@gmail.com

E. Papakonstantinou
Department of Food Science and Human Nutrition, Agricultural University of Athens,
75 Iera Odos, 11855 Athens, Greece
e-mail: emiliap@aua.gr; apapakonstantinou@gmail.com

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_32

MNT Medical nutrition therapy
NCP Nutrition care process
RR Relative risk
SCT Social cognitive theory

Introduction

Gestational diabetes mellitus (GDM) is defined as a "carbohydrate (CHO) intolerance of varying degrees of severity with onset or first recognition during pregnancy" [1]. More recently, GDM is defined as "diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes" [2]. GDM is one of the most common pregnancy complications with adverse health effects on both the mother and her offspring [2]. Moreover, development of type 2 diabetes among women with history of GDM has been found to be as high as 70% during a 10-year follow-up [3].

Medical Nutrition therapy (MNT) is the cornerstone for diabetes management. However, there is still insufficient evidence as to which is the optimal type of dietary advice in GDM [4]. The nutrition prescription (healthy food plan) should be individualized to each woman's needs, culture, weight gain, and physical activity and modified during pregnancy if necessary [4]. Although, there are few available randomized controlled trials (RCT) investigating the use of MNT in the treatment of GDM [5–7], they show beneficial effects of MNT for the mother and fetus, including improved glycemic control, appropriate gestational weight gain, lower frequency of insulin therapy, and fewer perinatal complications, such as neonatal hypoglycemia. Women with GDM should consume adequate energy to promote appropriate weight gain and adequate CHO, protein and fat based on the Dietary Reference Intakes (DRIs) for pregnant women [8, 9].

The Academy of Nutrition and Dietetics (AND) has developed GDM Evidence-Based Nutrition Practice Guidelines (http://andevidencelibrary.com/topic.cfm?cat=3719) and The GDM Toolkit which are designed to guide registered dietitians in the implementation of MNT for women with GDM. The Toolkit guides the registered dietitian to implement the nutrition practice guidelines within the framework of the MNT four step nutrition care process (NCP): nutrition assessment, nutrition diagnosis, nutrition intervention, and nutrition monitoring and evaluation. According to the GDM evidence-based Nutrition Practice Guidelines, MNT should be implemented within 1 week of diagnosis of GDM and requires a minimum of three visits to a registered dietitian. A summary of nutrition recommendations for women with GDM from various evidence-based publications is presented in Tables 32.1 and 32.2.

This chapter gives an overview of the dietary behaviors associated with GDM. It also discusses the limited nutrition knowledge among women with GDM reported by previous research, especially about CHO-containing foods. Finally, the chapter discusses the potential application of theories of behavior change in nutrition counseling to facilitate dietary behavior changes among women with GDM.

Dietary Behaviors Associated with Risk of GDM

Epidemiological studies have provided evidence that the incidence of GDM is increasing with the increasing burden of obesity among women of reproductive age [10]. Due to the limited number of studies that have examined dietary behaviors before or during pregnancy in association with GDM risk, there is an urgent need to identify risk factors for the prevention of GDM. Moreover, it is difficult

Table 32.1 Nutrition recommendations for appropriate weight gain, meal pattern, energy intake, and macronutrients for women with gestational diabetes mellitus [4, 8, 9, 22, 56]

Factors	Recommendation
Appropriate weight gain	Use body mass index (BMI) based on actual or estimated prepregnancy weight
Diet: Meals and snacks	Healthful diet consisting of unrefined or unprocessed grains or starches, lean meat or meat alternatives, fruits, and vegetables and dairy products Consume 3 meals and 2–4 snacks per day (one in the evening after dinner); eat every 2–3 h Daytime snacks should be eliminated in obese women with GDM to avoid food-stimulated insulin release Meal planning and timing of meals and snacks
Energy	Consume adequate calories to promote optimal gestational weight (minimum intake of 1600–1800 kcal/day) • Minimum weight gain of 7.0 kg for obese women (BMI > 29 kg/m^2) • For underweight women ($\leq$90% of desirable body weight (DBW)), 36–40 kcal/kg/day • For normal weight women (90–120% of DBW), 30 kcal/kg/day • For women $\geq$121–150% of DBW, 24 kcal/kg/day • For women $\geq$150% of DBW, 12–18 kcal/kg/day Weight loss is not recommended. If needed, caloric restriction ($\sim$70% of DRI) is safe without causing maternal or fetal compromise or ketonuria
Carbohydrates	Percentage depends on individual eating habits and effect on blood glucose goals • Maternal ketone testing is useful indicator in determining adequacy of maternal carbohydrate and/or energy intake • Carbohydrate intake should be 35–50% of total daily energy needs (minimum of 175 g/day) • Breakfast carbohydrates should not exceed 15–30 g • Limit foods creating a high glycemic response • The amount and distribution should be based on hunger, eating habits, weight gain, plasma glucose, ketone levels, and triglyceride concentrations • The amount of carbohydrates should be consistent at meals and snacks, especially in case of insulin therapy • Recommend low GI/GL carbohydrates
Protein	Adequate protein intake based on DRI for pregnant women • 20–25% of total energy intake (minimum intake of 60–80 g per day)
Fat	Adequate fat intake based on the DRI for pregnant women • 30–40% of total energy intake Limit saturated fat and replace with monounsaturated and/or polyunsaturated fats
Fiber	Daily consumption of 20–35 g

Legend Table 32.1 describes the current evidence-based nutrition recommendations of different Scientific Organizations, such as the Academy of Nutrition and Dietetics (AND), the American and European Diabetes Associations and others, for women with Gestational Diabetes Mellitus for appropriate weight gain, how many meals and snacks they should consume, what may be an optimal dietary pattern, as well as how much energy, macronutrients and fiber should be consumed

to draw definite conclusions from the existing literature since most of the studies examining the effects of diet during pregnancy on the overall health of the mother and fetus were cross-sectional or retrospective in design and the majority of them had very small sample sizes. These studies mainly focused on individual nutrients or a small number of foods [10]. However, foods contain a plethora of nutrients. Thus, results based on a single nutrient or food cannot account for the complex interactions of multiple nutrients in foods. Results from prospective studies have shown that higher fat intake and lower CHO intake may be associated with increased risk of GDM and impaired glucose tolerance [10, 11]. In a prospective study with 3063 pregnant Chinese women, the highest tertile of vegetable consumption pattern during pregnancy was associated with reduced risk of GDM [12]. Conversely, the highest tertile of sweets and seafood consumption pattern was associated with increased risk of

Table 32.2 Nutrition recommendations for micronutrients and other dietary components for women with gestational diabetes mellitus [4, 8, 9, 22, 56]

Vitamins/minerals	If usual dietary intake does not meet the DRI for pregnant women with GDM, vitamin and mineral supplementation is encouraged to prevent nutritional deficiencies • Include iron-rich foods • Include calcium-rich foods
Sodium	Sodium restriction has not been found to be beneficial in alleviating gestational hypertension
Alcohol	Consumption is not advisable during pregnancy, even in cooking
Caffeine	Limit caffeine intake
Sucrose and caloric sweeteners	Use depends on effect of blood glucose levels Avoid calorically sweetened beverage intake Sugar alcohols are safe when consumed within acceptable daily intake levels
Nonnutritive sweeteners	Should be consumed at moderation. They are safe when consumed within acceptable daily intake levels
Processed foods	Avoid processed foods
Fish	Incorporate low mercury content fish 2–3 times per week

Legend Table 32.2 describes the current evidence-based nutrition recommendations of different Scientific Organizations, such as the Academy of Nutrition and Dietetics (AND), the American and European Diabetes Associations and others, for women with Gestational Diabetes Mellitus for the major micronutrients, vitamins, alcohol, caffeine, sucrose, caloric sweeteners, nonnutritive sweeteners, processed foods, and fish consumption

GDM. Tables 32.3 and 32.4 summarize the findings of previous research that examined the effects of different dietary patterns and other nutrients on GDM risk [13–18].

Prepregnancy Dietary Factors and GDM Risk

Results from the Nurses' Health Study II identified two major dietary patterns, the "Western" and prudent [15]. The "Western" dietary pattern, characterized by high consumption of red meat, processed meat, refined grain products, sweets, French fries, and pizza was positively associated with GDM risk. On the other hand, the prudent dietary pattern, characterized by high consumption of fruits, green leafy vegetables, poultry, and fish was inversely associated with GDM, even after adjustment for major GDM risk factors, such as family history of diabetes and prepregnancy body mass index (BMI). The association between the "Western" dietary pattern and GDM risk was explained by the high consumption of red and processed meat products [15]. After adjustment for major risk GDM factors, women consuming more than six servings of red meat per week had more than 1.7-fold increased GDM risk compared to women consuming less than 1.5 servings of red meat per week [15].

Carbohydrate (CHO) Dietary Pattern, Dietary Fiber Intake, Glycemic Index (GI), and Glycemic Load (GL)

A study investigating the impact of CHO dietary pattern and its effects on the onset of GDM, reported that a prepregnancy low-CHO dietary pattern, characterized by high protein and fat intakes from animal food sources, was positively associated with GDM risk [13]. On the contrary, no association was found between prepregnancy low-CHO dietary pattern, characterized by high protein and fat intakes from vegetable food sources [18].

Table 32.3 Studies that reported associations of dietary factors and increased gestational diabetes mellitus (GDM) risk

References	Dietary pattern/Nutrient intake	Sample size	Results	Conclusion
Zhang et al. [16]	Dietary patterns	13,110	Relative risk (RR) of GDM, comparing the highest with the lowest quintile of the Western pattern scores, was 1.63. RR comparing the lowest with the highest quintile of the prudent pattern scores was 1.39. The RR for each increment of one serving/day was 1.61 for red meat and 1.64 for processed meat	A diet high in red and processed meat, refined grain products and sweets was associated with a significantly elevated GDM risk
Bao et al. [18]	Dietary protein pattern	21,457	RR of GDM for total red meat was 2.05. The RR for GDM for nuts was 0.73	A dietary pattern high in total red meat increases risk of GDM compared to diet high in vegetable protein
Chen et al. [21]	Added sugars	13,475	Compared with women who consumed less than 1 serving per month, those who consumed 5 servings or more per week of sugar-sweetened cola had a 22% greater GDM risk	Prepregnancy higher consumption of sugar-sweetened cola was associated with an elevated GDM risk
Bao et al. [13]	Low-carbohydrate dietary (LCD) pattern	21,411	Relative risk of GDM comparing highest with the lowest quartiles were 1.27 for the overall low-carbohydrate diet, 1.36 for the animal low-carbohydrate score and 0.84 for the vegetable low-carbohydrate score	A low-carbohydrate prepregnancy dietary pattern high in protein and fat from animal food sources was associated with increased risk for GDM
Bowers et al. [17]	Dietary fats	13,475	The substitution of 5% of energy from animal fat for an equal percentage of energy from carbohydrates was associated with significantly increased risk of GDM	Higher prepregnancy intakes of animal fat and cholesterol were associated with elevated GDM risk

Abbreviation: *RR* Relative risk

Legend Table 32.3 provides a summary of the some of the dietary patterns associated with increased GDM risk. A "Western" dietary pattern is high in red meat, processed meat and refined grain products. A "Prudent" dietary pattern is high in fruits, vegetables, poultry and fish. Red meat and processed were associated higher risk for GDM

Results from a prospective study investigating the associations between prepregnancy adherence to healthy eating patterns, characterized by high intakes of fruits, vegetables, whole grains, nuts and legumes, such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) as well as the Alternate Healthy Eating Index Diet (AHEI), and GDM risk, found significantly lower GDM risk with the adoption of one of the aforementioned healthy eating patterns [14].

Results from the Nurses' Health Study II showed that consumption of total dietary fiber, including fiber from grains and fruits, was associated with decreased GDM risk [16]. The association between dietary fiber and GDM risk may be explained by the fact that a high intake of dietary fiber may decrease appetite and desire for food intake, possibly leading to BMI reduction and improvement in insulin sensitivity [16]. Fiber intake may also act by delaying gastric emptying and slowing food digestion and absorption, thereby decreasing glucose absorption and plasma insulin levels.

Table 32.4 Dietary patterns associated with reduced gestational diabetes mellitus (GDM) risk

References	Dietary pattern/nutrient intake	Sample size	Results	Conclusion
Zhang et al. [16]	Dietary patterns	13,110	Relative risk (RR) of GDM comparing the lowest with the highest quintile of the prudent dietary pattern scores was 1.39	A prepregnancy diet high in fruits, leafy vegetables, poultry, and fish is associated with reduced risk GDM risk
Bao et al. [18]	Dietary protein pattern	21,457	RR for GDM for nuts is 0.73 while the RR for GDM for total red meat is 2.05	Substitution of vegetable protein, especially nuts for animal protein associated with lower risk of GDM
Tobias et al. [14]	(aMED), DASH, (aHEI) Dietary patterns	21,376	aMED was associated with a 24% lower risk, DASH with a 34% lower risk and aHEI with a 46% lower risk	Prepregnancy adherence to healthful dietary patterns was significantly associated with a lower risk of GDM
Zhang et al. [16]	Dietary fiber	13,110	Each 10-g/day increment in total fiber intake was associated with 26% reduction in risk in GDM	A prepregnancy dietary pattern high in total fiber and fruit and vegetable fiber was associated with an reduced GDM risk
Bao et al. [13]	Low-carbohydrate dietary pattern	21,411	Relative risk of GDM comparing highest with the lowest quartiles were 1.27 for the overall low-carbohydrate diet, 1.36 for the animal low-carbohydrate score and 0.84 for the vegetable low-carbohydrate score	Women of reproductive age who follow a low-carbohydrate dietary pattern may consider consuming vegetable rather than animal sources of protein and fat to minimize their risk of GDM

Abbreviations: *RR* Relative risk; *aMED* Alternate mediterranean diet; *DASH* Dietary approaches to stop hypertension; *aHEI* Alternate healthy eating index diet

Legend Table 32.4 provides a summary of some of some of the dietary patterns associated with reduced GDM risk aMED, DASH, and aHEI dietary patterns are characterized by high intakes of fruits, vegetables, nuts, and whole grains and lower intakes of in red meats. A Prudent dietary pattern is high in fruits, vegetables, poultry, and fish. These dietary patterns are associated with a reduced GDM risk. Conversely, a dietary pattern high in red and processed meat was associated with higher GDM risk

Each 10-g per day increment in total fiber intake was associated with a 26% decrease in GDM risk; whereas, each 5-g per day increment in cereal or fruit fiber was associated with a 23% GDM risk reduction [16].

The glycemic index (GI) and the related term glycemic load (GL) are qualitative and quantitative, respectively, measures of the glycemic response to dietary CHOs [19, 20]. The adoption of high GI/GL diet has been positively associated with GDM risk [16]. For example, it has been shown that the consumption of a high GI, low cereal fiber diet was associated with a 2.15-fold increase in GDM risk compared to a low GI diet high in cereal fiber [16].

Sugar-Sweetened Beverages and Risk of GDM

Results from the Nurses' Health Study II, after adjustment for all confounding factors (i.e. age, race, physical activity, smoking, alcohol intake, prepregnancy BMI, "Western" dietary pattern), showed that intake of sugar-sweetened cola was positively associated with GDM risk. Compared to women

who consumed one serving per month, those who consumed five servings per week of sugar-sweetened cola had a 22% greater GDM risk [21]. On the contrary, no significant association was found between other sugar-sweetened beverages or diet beverages and GDM risk.

Nutrition Knowledge of Women with GDM

It is well established that poorly controlled blood glucose in women with GDM increases their risk for maternal and neonatal complications [2]. CHO is the macronutrient with the greatest impact on postprandial blood glucose response. Increased postprandial blood glucose levels are associated with increased incidence of large-for-gestational-age infants and increased rate of cesarean sections [8]. Maternal hyperinsulinemia, with or without maternal hyperglycemia, is an important factor in fetal macrosomia [9]. Although the optimal amount of CHO for women with GDM is unknown, total intake should be individualized based on glucose tolerance, individual preferences and nutritional needs with a minimum intake of 175 g per day for provision of glucose to the fetal brain and prevention of ketosis [22]. It is important to note that CHO-containing foods such as milk, yogurt, fruits, cereal products, and starchy vegetables are important sources of energy, dietary fiber, vitamins, and minerals.

High CHO diets may lead to hyperglycemia, especially in women with GDM treated only with diet [23]. Nevertheless, total CHO restriction and low-CHO diets do not offer a metabolic advantage to women with GDM or their neonates [24] and may actually increase the risk of fetal macrosomia [25]. Thus, moderation of CHO intake is usually recommended as the first-line strategy to achieve optimal glycemic control among women with GDM [25]. Manipulating type and distribution of CHO in meals is the most common approach for GDM management.

Patient education on "Carbohydrate Counting" is encouraged as it has been shown to improve glycemic control with significantly fewer hypoglycemia [26]. However, it should be noted that there is a significant variation for practice between countries for the size of a standard carbohydrate portion with 10 g portions being the most common in Northern and Western Europe and 15 g portions being the most common in Southern Europe and the United States. Food records can be used to individualize a CHO-controlled meal plan for women with GDM. It is critical that women with GDM acquire knowledge about the CHO-containing foods to reduce risk of hyperglycemia. A limited understanding of the effects of dietary behaviors on blood glucose levels is likely to lead to low adherence to the individualized nutrition GDM treatment plan.

There are few available studies assessing women's knowledge of GDM. A study involving multiethnic women in the United Arab Emirates, investigated the knowledge of CHO-containing foods in a total of 184 pregnant women with and without GDM, found low levels of knowledge with no significant difference between women with and without GDM [27]. For example, the majority of women with GDM (86.2%) believed that whole wheat bread would not increase their blood glucose levels (Table 32.5). Furthermore, women with GDM in that study were found to have the least knowledge of three foods that contain CHO (unsweetened fruit juice, low fat milk and whole wheat bread) [27]. Another study conducted among 143 multiethnic women in Australia found low knowledge of CHO-containing foods, whereas knowledge about euglycemia and target blood glucose levels, hypoglycemia, and general knowledge about diabetes was adequate across the different ethnic groups [28]. On the other hand, results from a cross-sectional study involving 166 women with GDM in Malaysia reported highest knowledge scores for diet/food values domain and lowest knowledge score for management of GDM domain [29]. Spirito et al. [30] developed the Diabetes in Pregnancy Knowledge Screen (DPKS) questionnaire and assessed diabetes knowledge and pregnancy in 125 pregnant women (out of whom 56 with GDM). The results showed that women with GDM had low nutrition knowledge scores on the DPKS, indicating a strong need for additional educational support

Table 32.5 Carbohydrate-containing food knowledge of women with and without gestational diabetes mellitus (GDM) in the United Arab Emirates

Characteristic	GDM (n = 94)		Controls (n = 89)		P value*
	Correct response N (%)	Mean (SD)	Correct response N (%)	Mean (SD)	
Knowledge score**		8.65 ± 2.1		8.11 ± 2.1	0.112[a]
Low fat milk	16 (17)		9 (10.1)		0.165[b]
Honey	79 (84)		72 (80.9)		0.475[b]
White bread	85 (90.4)		63 (70.8)		0.001[b]
Pasta	79 (84)		73 (82.0)		0.716[b]
Rice	81 (86.2)		65 (73.0)		0.027[b]
Vegetable oils	54 (42.6)		44 (49.4)		0.350[b]
Unsweetened fruit juice	32 (34)		24 (27)		0.299[b]
Whole wheat bread	13 (13.8)		10 (11.2)		0.579[b]
Full fat milk	78 (83)		73 (82)		0.865[b]
Fresh fruits	36 (38.3)		30 (33.7)		0.518[b]
Leafy vegetables	88 (93.6)		80 (89.9)		0.358[b]
Chicken	62 (66)		67 (75.3)		0.167[b]
Meat	42 (44.7)		43 (48.3)		0.622[b]
Potato	80 (85.1)		66 (74.2)		0.065[b]

*$P < 0.05$ is considered significant

**Adjusted knowledge score using "educational level, nationality, age, parity, and number of visits to dietitian"

[a]P values calculated by Student t-test

[b]P values calculated by chi-square test

Legend This table shows no significant differences in the mean knowledge score of food sources of carbohydrate between women with GDM and that of pregnant women without GDM. A significantly higher proportion of women with GDM correctly identified rice and white bread as food sources of carbohydrate

Source Ali et al. [27]

in these women [30]. In the U.S., the Diabetes Prevention Program has shown the necessity of nutrition education in women with GDM and the positive impact of educational interventions to prevent progression from GDM to type 2 diabetes [31]. A U.S. cross-sectional survey study in 85 low-GDM risk pregnant women with only two nutrition questions, showed that prior to GDM diagnosis, women had knowledge that rice contains CHO and butter is a fat, as well as the importance of blood glucose control and exercise. However, their knowledge of the risk factors for GDM, treatment of GDM, causes of the condition and consequences to the mother and her offspring were low [32].

Among 120 antenatal women in a primary healthcare center in India, only a small proportion of rural antenatal women (17.5%) had good knowledge about GDM [33]. The main sources of nutrition information were family, friends, and television/radio. In a study involving multiethnic women in Australia, participation in web-based nutrition education intervention program improved significantly knowledge scores related to GDM, but to a lesser extent scores related to nutrition knowledge, including CHO-containing foods and other diet-related self-management principles [34]. Results from two studies that evaluated the relationship between nutrition knowledge and glycemic control reported an inverse association between knowledge scores and glycemic control [29, 33].

Factors Influencing the Nutrition Knowledge of Women with GDM

There are a number of factors associated with low nutrition knowledge among women with GDM, including ethnicity, beliefs and attitudes, lack of personal control over food choices, and health literacy level. Carolan et al. [28] assessed knowledge of GDM among multiethnic women in Australia in an effort to identify knowledge deficits across ethnic groups. Both ethnicity and educational level strongly influenced GDM knowledge. Thus, it appears that racial and cultural factors may have an impact on understanding of GDM and its management [28]. Studies that examined various ethnic groups have found that women's knowledge about GDM is often influenced by the experiences of others. For example, some women with GDM may feel that they will develop type 2 diabetes later in life, regardless of their effort in making significant lifestyle changes [35]. Among multiethnic women with GDM in the United Arab Emirates, perceived knowledge of diet and GDM was a significant predictor of CHO food knowledge score [27].

Some women with GDM may have little control over their meal planning and dietary behaviors, especially in certain populations where the influence of the cultural patterns of cooking, eating, and food sharing in social events is strong. Women with GDM may give a priority to the food preferences of their family members compared to their own dietary needs [35]. Less than 50% of multiethnic women with GDM in United Arab Emirates reported that they have "a lot of control" over food shopping, meal planning, and food preparation of their households [27]. One possible explanation for this finding is the dependence of these women on housemaids and the importance given to the food preferences of other members of the household [27]. Furthermore, health literacy and educational level may influence nutrition knowledge. For example, women with the highest educational scores have been shown to have a greater general comprehension about diabetes [28]. Finally, women with higher educational level sought greater access to scientific-based information compared with lower educational status [28]. Educational level was found to be the most significant predictor of GDM knowledge and glycemic control among women with GDM in Malaysia [29]. These findings indicate the need for educational strategies that have the potential to improve GDM management for women with lower literacy levels.

Challenges in Changing Nutrition Behaviors in Gestational Diabetes Mellitus (GDM)

Nutrition counseling is crucial for the management of GDM and various methods may be used. These include energy and CHO distribution in meals and snacks throughout the day, replacing higher GI/GL foods with low to medium GI/GL foods and training in carbohydrate counting [4, 5]. It has been proposed that pregnant women should receive nutritional counseling from the registered dietitian (RD) within 1 week after GDM diagnosis and should receive a minimum of three nutritional consultations [8]. Women who are placed on insulin need to be taught the signs and symptoms of hypoglycemia and treatment [9]. Most guidelines support that MNT is best prescribed by a dietitian or a qualified professional with experience in the management of GDM [4].

However, changing lifestyle behaviors, such as diet and physical activity levels, are a challenging task with many reported barriers. Women diagnosed with GDM may be motivated to make necessary lifestyle changes, particularly due to concerns regarding their offspring's health, although this is not always the case. Results of a study investigating perceptions of GDM showed contradictory data with some women perceiving GDM as a positive emotional motivator to help them adopt healthier lifestyle behaviors, while others perceiving it as a negative emotional barrier that interferes with their normal pregnancy experience [36]. Some women question GDM diagnosis, particularly those not requiring

insulin treatment [36]. One study reported that 31% of women with GDM treated only with lifestyle and 18% treated with oral medications or insulin perceived misdiagnosis of GDM [37]. Women with GDM may not be aware of their increased type 2 diabetes development risk later in life and thus, may not be motivated to adopt long-term healthy behaviors. Furthermore, studies have reported that some women with GDM may feel that GDM is only a temporary health condition which will be resolved after delivery [38–40]. These perceptions may hinder adherence to the recommended lifestyle changes during pregnancy and after delivery.

Healthcare professionals should emphasize to women with GDM the benefits of glycemic control during pregnancy as well as the importance of meeting their nutritional needs. Moreover, women should be encouraged to adopt long-term healthy lifestyle behaviors that minimize their future type 2 diabetes development risk. An important strategy to promote lifestyle behavior changes is to empower women by negotiating goals and increasing nutrition knowledge and skills. A patient-centered approach to counseling requires an active collaboration between the counselor and the patient so that the required changes can be achieved and maintained. Moreover, health professionals can facilitate lifestyle behavior changes by addressing the emotional aspects of GDM diagnosis and providing the necessary social support.

The teaching method used during nutrition counseling is as important as the nutrition information delivered to achieve the target behavior change goals and it should be an interactive process. Facilitating lifestyle behavior changes in women with GDM involves asking questions, discussing options for diabetes management and providing all the necessary tools in order to increase nutrition knowledge and empower the patient with options and skills. The method of asking questions can influence the patient's responses as well her motivation to make the required lifelong changes in dietary behaviors. Using open-ended questions promotes a trusting relationship and an open-dialogue with the patient. Health professionals need to show empathy and understanding of the patient's experiences and reactions. Moreover, it is important to discuss options for diabetes management with the patient. Involving the patient in decision-making, such as negotiating behavior change goals is crucial. The negotiated goals should be specific and realistic. The urgency of implementing these behavior change goals should be emphasized to prevent diabetes-related fetal and maternal complications. Empowering the patient with the necessary knowledge and skills is necessary in order for the patient to effectively implement the necessary changes and meet the agreed upon behavior changes. Using the information from the nutrition assessment and the nutrition diagnosis, the healthcare professional works with the patient to identify ways of implementing the identified goals and the required behavior changes to improve outcomes.

Applications of Behavior Change Theories in Nutrition Counseling for Women with Gestational Diabetes Mellitus (GDM)

The GDM evidence-based guidelines provide the framework for facilitating behavior changes in women with GDM (http://andevidencelibrary.com/topic.cfm?cat=3719). Although a variety of nutrition intervention approaches has been applied to promote optimal outcomes in GDM [41], application of the theory-based nutrition interventions is currently lacking. Thus, it is difficult to identify the most promising theory or model of behavior change that can be applied to GDM. However, given the success of application of behavior change theories and models in nutrition behaviors [42], it is a promising area for future research in GDM. A variety of behavior change theories and models exist. The healthcare professional needs to decide the most appropriate and relevant one to use with the patient during nutrition counseling keeping in mind that certain behavior change strategies are common to different behavior change theories and models. Two behavior change theories that have been applied to nutrition intervention programs are the Cognitive

Behavioral Theory (CBT) [43] and the Social Cognitive Theory (SCT) [44]. CBT assumes that behaviors can be changed by using both internal and external strategies, such as reinforcement, stimuli control as well as changes in the thought process. It involves using strategies that deal with the patient's cognition, perceptions, and thoughts to modify behaviors. Use of CBT has been associated with significant improvement in glycemic control in persons with type 2 diabetes [45]. Important counseling strategies for women with GDM include self-monitoring, goal-setting, social support, problem-solving, and reinforcement.

Social Cognitive Theory is based on the idea that people learn by observing other people [44]. An example of such a model involves the patient to participate in group education programs for GDM where participants share successful experiences of diabetes management. The dietitian serves as a role model by demonstrating specific tasks, such as how to read a food label or plan various healthful menus and asking the patient to perform a return demonstration. It is important to provide other good role models and avoid negative models.

Motivational Interviewing (MI) is a patient-centered style of counseling that has the potential to enhance readiness to change nutrition behaviors in GDM [46]. It is a useful tool for exploring the patient's attitudes and motivation to change nutrition behaviors. MI has been applied to various health-related conditions, including type 2 diabetes [47, 48]. Motivational Interviewing can be useful in exploring client's motivation, goals, challenges, and barriers to adopt the required nutrition changes and may provide a focused discussion plan on how to overcome perceived barriers. Patient's motivation can be enhanced by using a series of open-ended questions and listening to what is said and not said to understand the patient's feelings and attitude toward the required behaviors. It is important to note that the emphasis of applying MI in GDM is to increase patient's motivation rather than focusing on increasing knowledge. Although knowledge is a prerequisite for behavior change, it should not be expected to automatically lead to changes in nutrition behaviors of women with GDM.

Exploring the patient's attitudes toward the desired changes is a critical initial step in facilitating nutrition behavior changes in GDM. Nutrition counselors should explore the patient's attitudes, concerns, and perceptions, especially since some women may feel that GDM is a temporary situation and thus are not thinking about long-term changes in dietary behaviors. A summary of the key principles of MI is given in Fig. 32.1. One of the primary elements of MI is reflective listening [46]. Reflective listening encourages the patient to express thoughts and feelings about the target behaviors. It indicates to the patient that the counselor shows empathy, interest, and understanding. Thus, reflective listening can be used as a tool to build a trusting relationship with the patient, an essential element in establishing a long-term and collaborative relationship.

The Transtheoretical model (TTM) was developed by Prochaska et al. [49] and was originally designed for people with addictive behaviors, such as smokers. However, it has been applied to a number of health-related behaviors, including type 1 and type 2 diabetes [50]. A primary concept of this model is

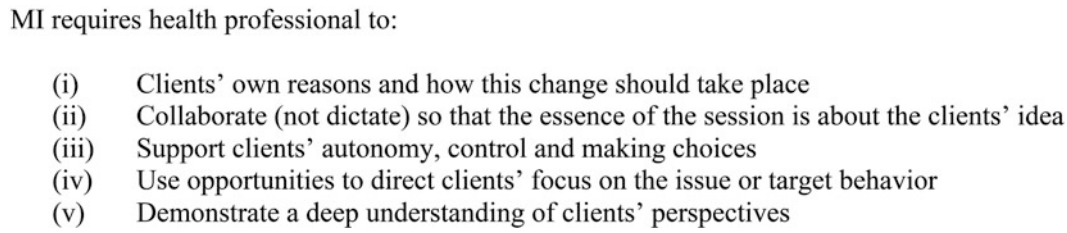


Fig. 32.1 The principles of motivational interviewing. This figure lists the main principles the health professional should follow when using motivational interviewing. Adapted from Decker et al. [57]. Publisher: American Psychological Association

the need to match the counseling to the patient's stage of readiness to change. For example, for a patient who is not interested in changing due to an attitude toward the desired behavior, an appropriate strategy is to explore attitudes through a series of open-ended questions. On the other hand, if the low motivation to change is a lack of awareness, increasing knowledge is an appropriate strategy to adopt. For a patient who is aware of the benefits of the desired changes but is ambivalent due to certain barriers, she will benefit the most from discussions about how to overcome these barriers. Moreover, the counselor can explore with the patient the benefits of the changes for her and her offspring.

Application of Behavior Modification Strategies in Gestational Diabetes Mellitus (GDM) Management

There are a number of behavior modification strategies that have the potential for facilitating nutrition behavior changes in women with GDM, including self-monitoring, problem-solving, goal-setting, and social support.

Self-monitoring is an important feature of behavior modification techniques used in cognitive behavioral theory (CBT) and Social Cognitive theory (SCT) [42]. Dietary self-monitoring has been associated with weight loss in lifestyle intervention programs [51]. Healthcare practitioners routinely ask women with GDM to monitor their blood glucose levels at home. On the other hand, self-monitoring of food intake and physical activity has received less attention compared to blood glucose self-monitoring. Dietary self-monitoring involves tracking food intake and triggers of the eating behavior to increase awareness about the current eating behavior. Although paper copy dietary records have been the principal strategy of dietary self-monitoring, new technologies including web-based, and smart phone food diaries can offer great opportunities for self-monitoring. Women with GDM should be encouraged to monitor their food intake and physical activity levels, as frequently as possible, along with their blood glucose levels in an effort to monitor the impact of food on glycemic control. The dietitian can review the records with the patient to identify patterns, to solve problems, and set realistic goals.
Problem-solving is a collaborative effort between the patient and the counselor. It is a useful tool in identifying barriers and searching for solutions. Application of problem-solving counseling strategy has been associated with improved diet in women with type 2 diabetes [52].
Goal-setting involves a collaborative working relationship between the counselor and the patient. It is an integral component of the nutrition care process as well a number of behavior change theories including CBT and SCT. Examples include

- "What do you think you can do?"
- "What will you do first?"
- "When will you be able to…?"
- "How will you do it?"

Reinforcement: Providing encouragement and praise to the woman with GDM can promote behavior changes. Positive reinforcement encourages behaviors to be maintained.
Social support: Support from health professionals, friends, and family is an important behavior change strategy for women with GDM in order to adopt and maintain nutrition behaviors that optimize pregnancy outcomes. The positive role of social support in facilitating lifestyle behaviors has been reported among women with type 2 diabetes and GDM [53]. It encourages the patient to seek support from family members, friends, and coworkers. Group education although often less intensive than individual counseling has been shown to be equally effective probably due to the positive aspects of social support [54].

Conclusions

Medical nutrition therapy (MNT) is a cornerstone in the management of GDM. MNT decreases adverse maternal and fetal outcomes. Moreover, nutrition counseling during pregnancy can assist in adoption of healthy dietary patterns that may reduce future risk of type 2 diabetes. Studies exploring the effects of dietary behaviors and risk of GDM have reported positive associations of dietary patterns characterized by high intake of animal fat, red meat, processed meat, refined grain products as well as sweets and increased GDM risk [10, 17]. On the other hand, dietary patterns high in fruits, green leafy vegetables, poultry, and fish were inversely associated with GDM. [15]. Dietary patterns high in fruits, vegetables, whole grains, nuts, and fish have been associated with reduced GDM risk [14].

CHO is the major nutrient affecting postprandial glucose levels. Manipulating type and distribution of CHO in meals is the most common approach in GDM management. For example, high fiber, low glycemic index/glycemic load diets have been found to have beneficial effects in the management of GDM [24, 25]. Thus, knowledge of CHO food sources may facilitate food choices that improve glycemic control. Previous studies reported limited nutrition knowledge in women with GDM with respect to CHO food sources and other dietary components [27, 28].

Applying behavior change theories in GDM management has the potential to facilitate changes in target nutrition behaviors [42]. It can assist in identifying patients' level of motivation as well as their potential barriers and facilitators [55]. It also provides the counselor an opportunity to explore strategies for overcoming the identified barriers.

Recommendations and Guidelines

Very few studies in the literature have examined dietary behaviors before or during pregnancy in association with GDM risk. Moreover, the majority of the studies examining the effects of diet during pregnancy on different health outcomes were cross-sectional or retrospective in nature and had very small sample sizes, which makes it difficult to draw definite conclusions from the existing literature [10]. Therefore, additional studies investigating dietary risk factors for the prevention of GDM are needed.

CHO is the macronutrient with the greatest impact on postprandial blood glucose response. Although the optimal amount of CHO for women with GDM is unknown, a minimum intake of 175 g per day for provision of glucose to the fetal brain and prevention of ketosis is recommended [22]. There is a need to increase nutrition knowledge of women with GDM, especially about food sources of carbohydrate and foods that are higher in fiber and low in glycemic index [27, 28]. It is important to apply the relevant behavior change theories including matching the client's stage of readiness to change with the appropriate counseling strategy [42]. Finally, studies involving use of behavior change theories to improve pregnancy outcomes of women with GDM are currently lacking and therefore, there is a need for future, more focused clinical trials, in this area.

References

1. Metzger BE, Coustan DR. Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 1998;21 Suppl 2:B161–7 (The Organizing Committee).
2. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(Suppl 1): S13–22.
3. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25(10):1862–8.

4. Moreno-Castilla C, Mauricio D, Hernandez M. Role of medical nutrition therapy in the management of gestational diabetes mellitus. Curr Diab Rep. 2016;16(4):22.
5. de Lima HT, Rosado EL, Neves PAR, Machado RCM, de Oliveira LM, Saunders C. Systematic review; Nutritional therapy in gestational diabetes mellitus. Nutr Hosp. 2013;28(6):1806–14.
6. Pastors JG, Franz MJ, Warshaw H, Daly A, Arnold MS. How effective is medical nutrition therapy in diabetes care? J Am Diet Assoc. 2003;103(7):827–31.
7. Reader D, Splett P, Gunderson EP, Diabetes C, Education Dietetic Practice G. Impact of gestational diabetes mellitus nutrition practice guidelines implemented by registered dietitians on pregnancy outcomes. J Am Diet Assoc. 2006;106(9):1426–33.
8. Academy of Nutrition and Dietetics. Gestational diabetes toolkit. The Gold standard companion to the Academy of Nutrition and Dietetics Evidence-Based Nutrition Practice Guideline. [DM-ROM] Chicago, IL, Academy of Nutrition and Dietetics. 2012.
9. Fagen C, King JD, Erick M. Nutrition management in women with gestational diabetes mellitus: a review by ADA's Diabetes Care and Education Dietetic Practice Group. J Am Diet Assoc. 1995;95(4):460–7.
10. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr. 2011;94(6 Suppl):1975S–9S.
11. Saldana TM, Siega-Riz AM, Adair LS. Effect of macronutrient intake on the development of glucose intolerance during pregnancy. Am J Clin Nutr. 2004;79(3):479–86.
12. He JR, Yuan MY, Chen NN, Lu JH, Hu CY, Mai WB, et al. Maternal dietary patterns and gestational diabetes mellitus: a large prospective cohort study in China. Br J Nutr. 2015;113(8):1292–300.
13. Bao W, Bowers K, Tobias DK, Olsen SF, Chavarro J, Vaag A, et al. Prepregnancy low-carbohydrate dietary pattern and risk of gestational diabetes mellitus: a prospective cohort study. Am J Clin Nutr. 2014;99(6):1378–84.
14. Tobias DK, Zhang C, Chavarro J, Bowers K, Rich-Edwards J, Rosner B, et al. Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. Am J Clin Nutr. 2012;96(2):289–95.
15. Zhang C, Schulze MB, Solomon CG, Hu FB. A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus. Diabetologia. 2006;49(11):2604–13.
16. Zhang C, Liu S, Solomon CG, Hu FB. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. Diabetes Care. 2006;29(10):2223–30.
17. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C. A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. Am J Clin Nutr. 2012;95(2):446–53.
18. Bao W, Bowers K, Tobias DK, Hu FB, Zhang C. Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: a prospective cohort study. Diabetes Care. 2013;36(7):2001–8.
19. Augustin LS, Kendall CW, Jenkins DJ, Willett WC, Astrup A, Barclay AW, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). Nutr Metab Cardiovasc Dis. 2015;25(9):795–815.
20. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34(3):362–6.
21. Chen L, Hu FB, Yeung E, Willett W, Zhang C. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. Diabetes Care. 2009;32(12):2236–41.
22. Marcason W. What is the appropriate amount and distribution of carbohydrates for a woman diagnosed with gestational diabetes mellitus? J Am Diet Assoc. 2005;105(10):1673.
23. Jovanovic L. Achieving euglycaemia in women with gestational diabetes mellitus: current options for screening, diagnosis and treatment. Drugs. 2004;64(13):1401–17.
24. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. Diabetes Care. 2014; 37(12):3345–55.
25. Louie JC, Brand-Miller JC, Moses RG. Carbohydrates, glycemic index, and pregnancy outcomes in gestational diabetes. Curr Diab Rep. 2013;13(1):6–11.
26. Schmidt S, Schelde B, Norgaard K. Effects of advanced carbohydrate counting in patients with type 1 diabetes: a systematic review. Diabet Med. 2014;31(8):886–96.
27. Ali HI, Jarrar AH, El Sadig M, Yeatts KB. Diet and carbohydrate food knowledge of multi-ethnic women: a comparative analysis of pregnant women with and without Gestational Diabetes Mellitus. PLoS ONE. 2013;8(9): e73486. doi:10.1371/journal.pone.0073486.
28. Carolan M, Steele C, Margetts H. Knowledge of gestational diabetes among a multi-ethnic cohort in Australia. Midwifery. 2010;26(6):579–88.
29. Hussain Z, Yusoff ZM, Sulaiman SA. Evaluation of knowledge regarding gestational diabetes mellitus and its association with glycaemic level: a Malaysian study. Prim Care Diabetes. 2015;9(3):184–90.
30. Spirito A, Ruggiero L, Bond A, Rotondo L, Coustan DR. Screening measure to assess knowledge of diabetes in pregnancy. Diabetes Care. 1990;13(7):712–8.

31. Gabbe SG, Landon MB, Warren-Boulton E, Fradkin J. Promoting health after gestational diabetes: a National Diabetes Education Program call to action. Obstet Gynecol. 2012;119(1):171–6.
32. Gastrich MD, Peck S, Janevic T, Bachmann G, Lotwala N, Siyam A. Gestational diabetes mellitus: an educational opportunity. J Diabetes Nurs. 2013;17(6):220–4.
33. Shriraam V, Rani MA, Sathiyasekaran BW, Mahadevan S. Awareness of gestational diabetes mellitus among antenatal women in a primary health center in South India. Indian J Endocrinol Metab. 2013;17(1):146–8.
34. Carolan-Olah M, Steele C, Krenzin G. Development and initial testing of a GDM information website for multi-ethnic women with GDM. BMC Pregnancy Childbirth. 2015;15:145.
35. Jones EJ, Appel SJ, Eaves YD, Moneyham L, Oster RA, Ovalle F. Cardiometabolic risk, knowledge, risk perception, and self-efficacy among American Indian women with previous gestational diabetes. J Obstet Gynecol Neonatal Nurs. 2012;41(2):246–57.
36. Parsons J, Ismail K, Amiel S, Forbes A. Perceptions among women with gestational diabetes. Qual Health Res. 2014;24(4):575–85.
37. Tang JW, Pumarino J, Cameron KA, Peaceman AM, Ackermann RT. Perceptions of misdiagnosis among women diagnosed with gestational diabetes. Diabet Med. 2015.
38. Hjelm K, Berntorp K, Apelqvist J. Beliefs about health and illness in Swedish and African-born women with gestational diabetes living in Sweden. J Clin Nurs. 2012;21(9–10):1374–86.
39. Collier SA, Mulholland C, Williams J, Mersereau P, Turay K, Prue C. A qualitative study of perceived barriers to management of diabetes among women with a history of diabetes during pregnancy. J Womens Health (Larchmt). 2011;20(9):1333–9.
40. Neufeld HT. Food perceptions and concerns of aboriginal women coping with gestational diabetes in Winnipeg, Manitoba. J Nutr Educ Behav. 2011;43(6):482–91.
41. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. Cochrane Database Syst Rev. 2013;3:CD009275.
42. Spahn JM, Reeves RS, Keim KS, Laquatra I, Kellogg M, Jortberg B, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. J Am Diet Assoc. 2010;110(6):879–91.
43. Ellis A. Overcoming destructive beliefs, feelings, and behaviors. Amherst, NY.: Prometheus Books; 2001.
44. Bandura A. Social foundations of thought and action: a social cognitive theory. Englewood Cliffs, NJ: Prentice-Hall; 1986.
45. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374–83.
46. Miller W, Rollnick S. Motivational interviewing: helping people change. 3rd ed. New York, NY.: Guilford Press; 2012.
47. Martins RK, McNeil DW. Review of Motivational Interviewing in promoting health behaviors. Clin Psychol Rev. 2009;29(4):283–93.
48. VanWormer JJ, Boucher JL. Motivational interviewing and diet modification: a review of the evidence. Diabetes Educ. 2004;30(3):404–6, 8–10, 14–6 passim.
49. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. Am Psychol. 1992;47(9):1102–14.
50. Jones H, Edwards L, Vallis TM, Ruggiero L, Rossi SR, Rossi JS, et al. Changes in diabetes self-care behaviors make a difference in glycemic control: the Diabetes Stages of Change (DiSC) study. Diabetes Care. 2003;26(3):732–7.
51. Burke LE, Wang J, Sevick MA. Self-monitoring in weight loss: a systematic review of the literature. J Am Diet Assoc. 2011;111(1):92–102.
52. Glasgow RE, Toobert DJ, Barrera M, Strycker LA. Assessment of problem-solving: a key to successful diabetes self-management. J Behav Med. 2004;27(5):477–90.
53. Yee LM, McGuire JM, Taylor SM, Niznik CM, Simon MA. Factors promoting diabetes self-care among low-income, minority pregnant women. J Perinatol. 2016;36(1):13–8.
54. Barrera M, Toobert DJ, Angell KL, Glasgow RE, Mackinnon DP. Social support and social-ecological resources as mediators of lifestyle intervention effects for type 2 diabetes. J Health Psychol. 2006;11(3):483–95.
55. Miller W, Rollnick S. Motivational Interviewing: preparing people for change. New York, NY.: Guilford Press; 2002.
56. Dornhorst A, Frost G. The principles of dietary management of gestational diabetes: reflection on current evidence. J Hum Nutr Diet. 2002;15(2):145–56; quiz 57–9.
57. Decker SE, Carroll KM, Nich C, Canning-Ball M, Martino S. Correspondence of Motivational Interviewing Adherence and Competence Ratings in Real and Role-Played Client Sessions. Psychological Assessment. 2013;25(1):306–12

Chapter 33
Higher Complex Carbohydrate Diets in Gestational Diabetes

Teri L. Hernandez

Key Points

- There remains no consensus worldwide on the optimal approach to nutrition therapy in women with GDM. Although the conventional approach has focused on carbohydrate restriction, there is no evidence from RCTs to support this practice in GDM.
- A balanced, effective macronutrient diet composition that includes a balanced liberalization of higher quality complex carbohydrates in GDM could improve maternal glycemia and concurrently prevent worsening of maternal metabolic parameters that lead to excessive fetal growth.
- A diagnosis of GDM generates maternal anxiety and fear for the offspring's well-being. Rigid control of diet through carbohydrate restriction has been identified as the most difficult component to treatment for GDM.
- Maternal anxiety in combination with rigid dietary carbohydrate restraint may lead to unintended consequences of nutrition therapy, such as compensatory higher fat intake.
- A carbohydrate's classification as *simple* or *complex* does not necessarily predict the postprandial glucose response.
- Liberalization of complex carbohydrates should emphasize higher quality carbohydrates that tend to be more nutrient dense (with more vitamins/minerals) are lower in calories, fiber, and glycemic index/glycemic load. It is not necessary to restrict all higher glycemic foods if the overall diet pattern is of higher quality.
- Major limitations of randomized studies in GDM to date include dietary noncompliance, confounding insulin therapy, and inconsistent reporting of BMI and gestational weight gain.
- The evidence from RCTs in GDM implies that a balanced liberalization of higher quality complex carbohydrates results in good maternal glycemic control, improved lipemia, vascular benefits, improved insulin action, and improved glucose tolerance despite the background of pregnancy-induced insulin resistance. Low-GI diets may reduce the need for insulin and lower postprandial glycemia.

Keywords Gestational diabetes · Diet · Nutrition · Glycemic index · Complex carbohydrates · Diet quality · Glucose · Insulin resistance · Glycemia

T.L. Hernandez (✉)
Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes,
University of Colorado, Anschutz Medical Campus, 12801 E. 17th Avenue, Mail Stop 8106,
Aurora 80045, CO, USA
e-mail: teri.hernandez@ucdenver.edu

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_33

Abbreviations

AUC	Area-under-the-curve
BMI	Body mass index
DASH	Dietary approaches to stop hypertension diet
FFA	Free fatty acids
GDM	Gestational diabetes mellitus
GI	Glycemic index
GL	Glycemic load
LGA	Large-for-gestational-age
RCT	Randomized clinical trial
TG	Triglycerides

Introduction

Nutrition therapy is the original and most potent approach to treatment of diabetes, thus it remains the foundational method for management of gestational diabetes mellitus (GDM). As the phenotype of hyperglycemia in pregnancy shifts due to new diagnostic criteria, and the prevalence of GDM increases to 20% of pregnancies [1], nutrition therapy is the single treatment component that will reach every woman with the diagnosis. If effective, good nutrition in GDM can support gestation and maintain euglycemia while avoiding the need for costly additive medication [2], setting the stage for optimal lifetime health and nutrition for the offspring [3].

The conventional approach to nutrition therapy in GDM is focused on carbohydrate restriction [4]. Although restriction of dietary carbohydrate reduces postprandial hyperglycemia, decreases fetal glucose exposure, and lessens the risk for macrosomia [5], it is perhaps the most difficult element to treatment adherence in GDM [6]. Despite the long clinical experience with carbohydrate restriction in diabetes management [7], there is a lack of evidence supporting carbohydrate restriction in GDM [8, 9]. Moreover, new concerns focused on unintended consequences of carbohydrate restriction in pregnancy have been recognized [2, 8, 10]. Particularly in obesity-promoting environments, with carbohydrate restriction, come a high potential for increased dietary fat intake. Growing evidence supports that maternal lipids [triglycerides (TG), free fatty acids (FFA)] are highly associated with excess fetal growth [11]. In 2005, the American Diabetes Association withdrew nutrition therapy guidelines for GDM [8]. More than 10 years later, there remains no consensus in the United States (Table 33.1) or worldwide [9] on the optimal approach to nutrition therapy in women with GDM. There remains a need for highly controlled randomized trials focused on understanding the physiologic effects *beyond glucose* of nutritional approaches to therapy in GDM [2, 8].

Fortunately, evolving science has confirmed a differential impact of dietary carbohydrate on postprandial glucose [12]. In general, carbohydrates have gained notoriety due to the potency of simple sugars to acutely raise blood glucose [13]. However, *carbohydrate* as a macronutrient descriptor includes a wide range of different compounds. Importantly, some *complex carbohydrates* are now recognized as polysaccharides and starches (primarily from grains, vegetables, and legumes) that are more nutrient-dense [14] and tend to lessen a sharp rise in postprandial glucose [15]. In theory, then, if women with GDM choose the right kinds of dietary carbohydrates, nutrition therapy could safely include more carbohydrate instead of less, while still supporting healthy gestation and meeting targets for glycemic control. In this chapter, background on dietary carbohydrate will be reviewed as it applies to GDM and its underlying physiology. Then, evidence from randomized trials that supports a balanced liberalization of complex carbohydrate within nutrition therapy approaches for women with GDM [6] will be reviewed.

Table 33.1 Lack of consensus across nutrition therapy recommendations in the United States

ADA 5th International Workshop-Conference on GDM 2005 [8]	American College of Obstetricians and Gynecologists 2013 [80]	The Endocrine Society 2013 [81]	ADA Medical Nutrition Therapy 2013 [82]	American Heart Association/ American College of Cardiology 2013 [83]
– Insufficient evidence – Recommendations withdrawn	Carbohydrate: 33–40%	Carbohydrate: 35–45%	– Inconclusive evidence – Individualization recommended	Carbohydrate: 55–59% Fat: 26–27% Saturated fat: 5–6% Protein: 15–18%

Comparison of nutrition therapy recommendations for GDM from the American Diabetes Association (ADA), American College of Obstetricians and Gynecologists, and Endocrine Society. Recommendations from the ADA for diabetes outside of pregnancy, and from the American Heart Association/American College of Cardiology (AHA/ACC) for cardiometabolic health outside of pregnancy are included for comparison. The AHA/ACC evidence-based recommendations support a balanced liberalization of higher quality complex carbohydrates in combination with lower fat, moderate protein, and higher overall diet quality to reduce risk for cardiometabolic disease. Although the recent ADA guidelines do not specify liberalization or restriction of any particular macronutrient, higher overall diet quality is emphasized

Diabetes Begets Diabetes: Nutrition Therapy Can Break the Cycle

Pioneers in obstetrics and diabetes recognized that in utero environmental conditions are shaped by maternal nutrition [16]. Thus, manipulation of maternal metabolism using good nutrition is a priority in the pursuit of optimal infant outcomes. Normal metabolism in pregnancy is a synchronized adaptation designed to ensure nutrient delivery to the fetus while supporting maternal metabolic needs. It is characterized by impaired insulin sensitivity, increased postprandial glucose [17], a two–threefold increase in insulin production [18], and coordinated increases in circulating FFA, TG, total cholesterol, and phospholipids [17, 19]. By the third trimester, insulin resistance increases markedly each week, shunting more nutrients away from mother to the fetus. It is thought that overweight/obese women, particularly those who develop GDM, enter pregnancy with a "background" of chronic preexisting insulin resistance, upon which the insulin resistance of normal pregnancy is additive [18]. Overweight and obese women display exacerbated impairments in insulin-stimulated glucose utilization, insulin suppression of hepatic glucose production, and insulin suppression of plasma FFA by the third trimester [18–21].

The concept that *diabetes begets diabetes* has long been recognized in association with the high prevalence of offspring diabetes linked to in utero exposure to (preexisting) maternal diabetes [22]. Likewise, it is appreciated that GDM also has potential to create a persistent cycle of obesity and diabetes prevalence. Up to 50% of mothers with GDM will develop type 2 diabetes within 10–20 years [23]. Moreover, the offspring of women with GDM are at risk for LGA (large-for-gestational-age; $\geq$90th percentile) [24], increased adiposity [25, 26], impaired glucose tolerance [27], metabolic syndrome [28], and type 2 diabetes [25, 29]. Larger newborns are more likely to become obese adults [24, 30], and females born LGA have a doubled risk for delivering a LGA infant themselves [31]. Thus, women with GDM perpetuate an intergenerational cycle of obesity and diabetes prevalence, particularly when an affected daughter becomes pregnant [32]. The connection between obesity and diabetes generational cycles and in utero nutrient exposures has been strongly supported in both animal and human models [33].

A balanced, effective macronutrient diet composition in GDM could improve maternal glycemia and concurrently prevent worsening of maternal metabolic parameters that lead to excessive fetal

growth. Moreover, an optimal macronutrient mixture could promote the inception of healthy lifetime nutrition [3] in the offspring. Heightened maternal insulin resistance and lipolysis are key features to the maternal physiological adaptation in pregnancy, such that the liberated FFA support maternal metabolism as glucose is preferentially shunted to the placenta/fetus. The average lifespan of an adipocyte is ~10 years, and during that time the adipocyte will completely turnover its stored FFA only ~6 times [34, 35]. Thus, the nutritional pattern long before conception determined the quality of FFA stored in maternal adipose tissue by the time pregnancy occurs. Despite the adaptive insulin resistance of pregnancy, theoretically, an optimal mixture of more nutrient-dense complex carbohydrates with less glycemic potential, lower fat, and appropriate protein in the context of higher overall diet quality hold potential for promotion of good glycemic health while meeting pregnancy nutritional goals. Nutrition therapy in GDM, therefore, holds great potential to effectively treat this growing population of mothers and offspring, optimizing the intrauterine environment to break the intergenerational cycle of diabetes prevalence.

Anxiety, Rigid Adherence, and Unintended Consequences

A diagnosis of GDM generates anxiety that may lead to unintended consequences of nutrition therapy. Until GDM is diagnosed at ~28 weeks gestation, women feel they have experienced a "normal" pregnancy over which the development of GDM has occurred asymptomatically [36]. The diagnosis suddenly assigns a high-risk pregnancy label, requires "diet" adherence, heightened medical surveillance, potential treatment with insulin, and self-monitoring of glucose. Women have reported that the GDM diagnosis generated fear for the well-being of the baby, anxiety, and depression [36, 37]. Nutrition therapy itself has been described as intrusive [36], and an infringement on cultural/social beliefs and usual dietary eating patterns [37, 38]. Rapid adaptation late in pregnancy is challenging [36, 39], and food selection is mentally taxing [39].

The conventional approach to nutrition therapy in GDM has focused on rigid restriction of dietary carbohydrate and blood glucose control. In general, rigid adherence to a "diet" is associated with high internal self-pressure and a focus on forbidden foods [40] that undermines weight loss and nutrition interventions. Conversely, *flexible* eating restraint allows that no behaviors or foods are forbidden. This approach helps alleviate the feeling of rigid control, lessens internal self-pressure, and allows a range of behaviors and foods that are acceptable. Psychological flexibility, including flexible eating restraint, is associated with better health/psychological well-being, higher self-determination, and commitment to personal health goals, all of which predict success for nutrition therapy [40].

In the author's clinical experience, women with GDM were extremely fearful of macrosomia. They associated carbohydrate as the cause of macrosomia and reasoned that less carbohydrate would result in a better infant outcome. They followed extreme carbohydrate-restricted diets, opting to replace carbohydrate calories with those from fat. This rigid practice resulted in controlled glycemia. However, they were anxious, unhappy, and consumed only a narrow range of acceptable foods. Pregnant women should consume at least 175 g of carbohydrate/day, of which ~30 g support fetal growth/brain development [41]. Extreme carbohydrate restriction carries a risk for maternal ketosis [42] due to less insulin suppression of lipolysis [43]. This practice could also compromise the obligate fetoplacental glucose supply, which is dependent on the maternal-fetal gradient and requires higher maternal glucose for transfer [44]. Population studies have shown that protein intake tends to be stable in humans [45], and in pregnancy, controlled studies of protein supplementation suggested that high protein intake was associated with reduced infant birth weight [3]. Thus, with three macronutrients, if carbohydrate is restricted and protein remains stable, the remaining calories would come from fat. This is concerning for several reasons. Outside of pregnancy, rigid carbohydrate restriction (20 g/day) with high-fat intake resulted in sustained elevated FFA over 24 h and almost complete

lack of FFA suppression by insulin [46]. In studies of women during late pregnancy, elevated FFA with lipid infusion, simulating high-fat postprandial conditions, contributed to worsening peripheral and hepatic insulin resistance [21]. Mounting evidence supports a potential deleterious intrauterine programming effect of lipids/fatty acids on abnormal fetal growth patterns and poorer long-term infant health [33]. Taken together, an approach to nutrition therapy in GDM that includes a balanced liberalization of complex carbohydrates in the context of flexible eating restraint could help mitigate anxiety and avoid unintended consequences associated with compensatory higher fat intake.

Classification of Carbohydrates

Newer evidence has confirmed that the association between the type and amount of dietary carbohydrate and glycemic response is more elusive than previously believed, and this has prompted a movement away from conventional nomenclature that has described carbohydrates for decades. The term *complex carbohydrate* was first coined within the 1977 U.S. Dietary Goals recommendations [15]. Classification of carbohydrates by their chemical structure and molecular weight resulted in two overall categories: *simple sugars,* including 1-, 2-, or 3-carbon carbohydrates with lower molecular weights (i.e., glucose, fructose, sucrose); and *complex carbohydrates*, the higher molecular weight polysaccharides with long carbon chains, including the components *starch* and *fiber* in foods such as vegetables, whole grains, and legumes [47]. For decades, these classifications of carbohydrates fueled the maxim that glycemic response could be predicted based on the chemical structure of the molecule. It was reasoned that larger carbohydrate molecules should require a longer digestive time course, leading to slower release/absorption of post-digestive monosaccharides, mitigating a sharp increase in postprandial glucose [15].

It is now understood that carbohydrate classification does not necessarily predict the postprandial glucose response. In fact, the association is *nonlinear* instead of linear, in which a smaller molecule would always predict a higher glycemic response, and vice versa. For example, simple sugars have long been implicated in driving higher glycemic responses. However, fructose does not acutely raise glucose, and sucrose produces a moderate instead of higher glucose [13]. Whole grains are considered complex carbohydrates, but can result in a higher glycemic response if the grain seed is modified or sugars are added [14, 15]. Moreover, with total carbohydrate held constant, the complex carbohydrates corn and rice produce a lesser glycemic response compared to categorically similar potatoes and bread [48]. Fiber is thought to slow digestion and result in less glycemic response, particularly viscous fiber [12]. Fiber can be nondigestible (from plants), digestible, or functional, meaning their nondigestible components have been isolated/extracted to produce a beneficial physiologic impact [14, 15, 47]. However, recent data from highly controlled meal studies revealed that fiber had little or no association with glycemic response, either as a single food or within a mixed meal [49]. Many, but not all, whole grains are sources of dietary fiber [14], thus it cannot be assumed that all complex carbohydrates are fiber rich. Moreover, equal amounts of carbohydrate could result in up to a fourfold difference in glycemic response within and between individuals due to factors such as digestibility, food processing, biological characteristics, and interaction with other macronutrients (fat, protein) [15]. Thus, the association between the type of carbohydrate and postprandial glucose response is nonlinear. Use of the terms *complex carbohydrate* and *simple sugar* in the context of glycemic management has undergone scrutiny as understanding of these associations has evolved.

Glycemic Index, Glycemic Load, and Carbohydrate Quality

Glycemic index, glycemic load, and carbohydrate quality are key concepts for consideration in an approach to nutrition therapy in GDM that includes a balanced liberalization of complex carbohydrates. These concepts have been a source of notoriety over the past two decades, largely driven by concerns over methodological issues, interpretation, and application of the glycemic index (GI) [12, 15, 48]. GI is a property of a carbohydrate food that describes its blood glucose raising potential: a low-GI food has a less potent ability to raise postprandial glucose, while high-GI foods acutely raise blood glucose [13] (Table 33.2). It has been demonstrated that lower GI foods produce higher satiety, while higher-GI foods are associated with increased hunger and energy intake [13]. Importantly, the GI must be measured and cannot be estimated based on the classification of a carbohydrate. A related concept is the glycemic load (GL) (Table 33.2), which describes the global insulin demand created by a carbohydrate food [48]. Finally, the concept of carbohydrate quality has gained importance as population eating patterns have increasingly included refined, processed foods high in sugars and fats in parallel with the heightened prevalence of obesity, insulin resistance, and diabetes. *Higher quality* carbohydrates tend to be more nutrient dense (i.e., contain more vitamins/minerals), are lower in calories, fiber, and GI/GL [13, 14].

Population evidence supports the association between postprandial hyperglycemia and cardiovascular mortality both within and outside of diabetes [13, 50]. Starting in the normal range and increasing to hyperglycemia, postprandial glucose is described to exert pulsatile-like forces that promote oxidative stress, thrombosis-activating factors, and endothelial dysfunction [13, 15]. In recent years, a focus on low-GI foods for nutrition in pregnancy has gained popularity [51]. In seminal studies, Freinkel [16] described that postprandial glycemia in pregnancy is exaggerated, coined *facilitated anabolism,* by which the post-meal glucose increases the maternal-fetal glucose gradient, allowing placental transport. Thus, in pregnancy, maternal postprandial glucose "feeds" the fetus. Because postprandial glycemia is higher with heightened insulin resistance and impaired glucose tolerance (i.e., obesity, GDM, preexisting diabetes), and these conditions are associated with higher birth weight [5], the conventional focus on carbohydrate restriction is meant to target this process to reduce the risk of macrosomia/LGA [2]. The impact of a balanced liberalization of complex carbohydrates on postprandial glycemia, then, is critically important for GDM because the right type of complex carbohydrates must be promoted. Based on several levels of international consensus, these complex carbohydrates should be of *high quality* [13, 14]. Recognizing that it is not necessary to exclude all higher-GI carbohydrates, inclusion of more high quality carbohydrates can be part of an overall heart-healthy healthy eating pattern [52, 53]. Thus, the balanced liberalization of complex carbohydrates in nutrition therapy for women with GDM must emphasize those with higher quality.

Table 33.2 Ranges of glycemic index and glycemic load [48]

	Glycemic index[a]	Glycemic load[b]
Low	≤ 55	≤ 10
Medium	56–69	11–19
High	≥ 70	≥ 20

[a]Defined as the incremental glucose area-under-the-curve after ingestion of a 50 g serving of available (digestible) carbohydrate; expressed as a percentage of the incremental glucose area-under-the-curve of a 50 g portion of a reference food (available carbohydrate: glucose, white bread, where GI = 100) [13, 52, 84]
[b]Defined as: GI x carbohydrate/serving/100 [15, 48]

Evidence Supporting Complex Carbohydrates in Nutrition Therapy for GDM

Given the reviewed background considerations for nutrition therapy in GDM, the available evidence from RCTs to date will be reviewed that supports implementation of a balanced liberalization of higher quality complex carbohydrates. Ten trials met strict criteria listed in Table 33.3. The evidence

Table 33.3 Ten randomized clinical trials (RCTs) met strict criteria for inclusion in this evidence review

Criteria for inclusion	Overall trial characteristics
1. Prospective, randomized clinical trial (RCT) 2. Included women with a GDM diagnosis after 24 weeks but by the 3rd trimester 3. Independent variable was diet exposure in which the type or amount of carbohydrate was varied 4. Diet exposure lasted >24 h 5. The macronutrient distribution was reported and/or actual intake was reported 6. A measure of diet adherence was included *OR* food was provided 7. Diets were eucaloric 8. Studies were free of confounding anti-hyperglycemic medications (insulin, glyburide, metformin) – *OR* the analysis was conducted with and without those on medication – *OR* the use of medication was predefined as the primary outcome 9. The report was published in English	– 10 RCTs – 609 women with GDM across 6 countries Australia [54, 58, 71] United States [56, 59] Poland [60] Iran [62–64] Spain [61] China [55] – GDM diagnostic criteria: American Diabetes Association, World Health Organization, Australian Diabetes in Pregnancy Society, National Diabetes and Pregnancy Clinical Guidelines, International Association of the Diabetes and Pregnancy Study Groups – Diet exposures ranged 3 days–15 weeks Beginning at 24–31 weeks gestation – Carbohydrate intake ranged 35–70% of total calories Fat 10–45% Protein 15–25% – Six trials had a primary outcome on which the study was powered (n = 372 women) [56, 58, 59, 61–64]. Primary outcomes (not necessarily powered endpoints) ranged from glycemic control, need for insulin therapy, to infant birthweight – BMI Non-Asian: 25–34 kg/m^2 Asian: 20–21 [55], 24 kg/m^2 (50% of sample in [58]) Not reported in 2 trials [59, 60] 3 trials reported only pre-pregnancy BMI and not at the time of nutrition intervention [55, 58, 61] – Gestational weight gain With one exception [61], gestational weight gain was not different between diet exposure groups Only three trials reported gestational weight gain during the actual intervention [57, 62–64] Others reported total gestational weight gain [58, 59, 61] – 2 RCTs did not report gestational weight gain [60, 71] Weight gain was not reported in 2 trials that were short crossover exposures (3–4 days) [54, 56], and 1 trial that was a 4-day exposure where GI was manipulated [55] – One group published data twice from the same study according to identical trial numbers [62, 63]; they were counted as one study – Two RCTs included follow-up in a second publication [57, 72]
Salient points for evidence interpretation	
– Only ~50% of the represented women participated in an appropriately powered trial, making negative findings difficult to interpret (increased chance of a Type II error) – Interventions varied widely across a range of carbohydrate intake – Trials involved manipulation of either total amount or type of carbohydrate intake (i.e., complex carbohydrates, GI) – Trials included mostly Caucasian women, with representation of Persian and Asian women across a heterogeneous range of diagnostic criteria – BMI encompassed normal-weight through Class I obesity [85] – Gestational weight gain was not consistently reported; it tended to be reported as total instead of what occurred during the intervention itself – Compliance was as low as 50% and was assumed to be high in trials where all food was provided; however, despite measures in place to encourage/measure compliance, it is difficult to assess true diet adherence across most of the studies	

Criteria for inclusion are listed on the left. Overall characteristics of the 10 RCTs are listed in the right column. The lower left column offers salient points to consider when interpreting evidence from the trials

for liberalization of complex carbohydrates spoke to seven salient themes for discussion: (1) Compliance with nutrition therapy; (2) Effects of higher complex carbohydrate diets on maternal glucose metabolism; (3) Metabolic effects of higher carbohydrate diets beyond maternal glucose; (4) Need for insulin therapy; (5) Maternal/infant outcomes; (6) Fiber and GI; and, (7) Gestational weight gain.

Compliance to Nutrition Therapy. Compliance to nutrition therapy in GDM remains one of the largest confounding factors across studies [2]. Across the 10 RCTs (Table 33.4), three studies provided food to the participants [54–57], and one group provided a sample food basket [58]. Other strategies to ensure adherence included use of compliance tools with scoring and/or a questionnaire, self-reported intake through food records, phone follow-up, meetings with a registered dietitian, and providing menus for participants to follow. However, in the 7 studies where food was not provided there were some notable limitations created by reduced compliance. Reece [59], manipulated fiber content (80 g fiber/60% total carbohydrate vs. 20 g fiber/50% total carbohydrate) and there was no difference in glycemic control. However, compliance was 60% "good" and 40% "acceptable," and there was significant attrition. Cypryk et al. [60] compared 60–45% total carbohydrate content and found improved glycemic control within groups, but compliance was ~50%. Despite providing sample food baskets, participants in the study of Louie et al. [58] failed to achieve the GI targets, resulting in little difference between diet exposures (GI: 53 vs. 47) that could have influenced the negative trial outcome. In Spain [61], higher versus low-carbohydrate interventions were compared in relation to the need for insulin therapy; only 63–67% of women returned diet records and only the low-carbohydrate group met the carbohydrate target. Moreover, attrition within the control group was 20% (vs. 7%). In studies where the Dietary Approaches to Stop Hypertension (DASH) low-sodium diet was compared to a control diet, urinary sodium could have been used to measure compliance, but was not included [62–64]. Even within the remaining studies where compliance strategies were reported, adherence was not rated per se. In the single study where food was provided for consumption in the free-living environment [56, 57], full compliance still cannot be guaranteed. Largely these examples underscore the critical need to consider compliance as a factor in the interpretation of trial outcomes.

Higher Carbohydrate Diets and Maternal Glucose Metabolism. The conventional approach to treatment of GDM has focused on rigid control of maternal glucose, usually with treatment targets of: fasting $\leq$95 mg/dL, and $\leq$140 or $\leq$120 mg/dL for 1- and 2-h postprandial glucose, respectively [65]. Typically, women with a fasting glucose $\leq$95 mg/dL are able to achieve acceptable glycemic control using nutrition therapy alone within 2 weeks of diet prescription [66]; fasting glucose >105 mg/dL is predictive of the need for insulin therapy [67]. Using a strong crossover study design, two smaller RCTs in which all food was provided demonstrated that liberalization of higher quality complex carbohydrates to 60–70% of total intake controlled postprandial glucose to within treatment targets in as quickly as 3 days (n = 4 women) [56] and 4 days (n = 16) [54]. Although maternal glucose control might in part be explained by fiber in one study (70 g fiber, 70% carbohydrate vs. 31 g, 35% carbohydrate) [54], fiber was similar the other study (29 g, 60% carbohydrate vs. 24 g, 40% carbohydrate) [56]. Moreover, it should be noted that in the second study [56], although total potential fetal glucose exposure over 24 h was 6% greater on the 60% higher complex carbohydrate diet (vs. 40% carbohydrate), both exposures controlled maternal glycemia to acceptable levels. Cypryk et al. [60] similarly demonstrated within a 60% total carbohydrate exposure group over 14 days that postprandial glucose was lower than baseline. Unfortunately, the change in glycemia was not compared to the lower carbohydrate exposure group, and compliance was low (50%).

In Persian women, complex carbohydrates were liberalized to 65–67% using the DASH diet (vs ~55% carbohydrate diet; 4-week intervention; began gestational week 24–28). Women with GDM demonstrated improved response to an oral glucose tolerance test [62] and a decreased fasting glucose [63] (Table 33.4). It is noted that the DASH diet was similar in carbohydrate, sugars, and fiber to the 60% diet exposure used in the U.S. [57], from which similar findings were reported.

Table 33.4 Randomized controlled trials of nutrition interventions for diet-controlled GDM in which type or amount of carbohydrate was manipulated

Study	Design/*N* Maternal BMI[a] (kg/m^2)	Primary outcome Power	Intervention	Exposure length	Compliance	Maternal outcome[b]	Infant outcome[b]	Conclusion/Comment
Nolan [54] Australia	Randomized crossover *N* = 4 26.9 ± 8	Blood/urine glucose, blood insulin, FFA, TG, TC Pilot study Not powered	HC: 70/10/20 70 g fiber LC: 35/45/20 31 g fiber – Unrefined CHO on both	4d each Begin 33.4 ± 1.4 week No washout	– Food provided – Hospital admission	HC: – Fasting TC 6% lower – Fasting FFA 14% lower -Improved 50 g OGTT response (day-4)	–	– HC diet associated with improved glucose tolerance, FFA, TC versus LC – Plasma glucose similar between diets but only 3 measures/day
Reece et al. [59] United States	RCT *N* = 50 total *N* = 22 GDM 11 High fiber 11 ADA Data from GDM only BMI not reported	Difference in glycemic control (average SMBG, 6x/day) Powered on 20% difference between groups	High fiber: 60/20/20 80 g fiber ADA: 50/30/20 20 g fiber	10–15 week Begin 24–29 week	– Dietary Compliance Tool – 60% good – 40% acceptable – 11 dropped out across groups; details not reported	*Mean BG* High fiber: 88 ± 10.6 mg/dL ADA: 88 ± 9.1 mg/dL *Total GWG* High fiber: 14.3 ± 6.8 kg ADA: 11.9 ± 3.8 kg [Mean ± SD (assume SD), *p* = NS for all]	*BW* High fiber: 3519 ± 475.9 g ADA: 3613 ± 360.2 g *GA* High fiber: 39 ± 1.9 week ADA: 39 ± 1.1 week [Mean ± SD (assume SD), *p* = NS]	– No difference in glycemia, maternal or infant outcomes – GDM group: SMBG 6x/day on only 2 days/week – Unclear if GDM women dropped and which week – 7 more women did not keep diet records; compliance tool could not be used
Cypryk et al. [60] Poland	RCT *N* = 30 15 LC 15 HC BMI not reported	Difference in blood glucose, urine ketones Not powered	HC: 60/15/25 LC: 45/30/25	14 days Begin 29.2 ± 5.4 week	– Compliance questionnaire – About 50% compliance on each diet	LC/HC: – Postprandial glucose across meals lower versus baseline – Glucose lower on HC but was not compared to LC – GWG not reported but stated appropriate	*BW* LC: 3407 ± 309 38.9 ± 1.4 week HC: 3385 ± 418 38.8 ± 1.2 week *GA* LC: 38.9 ± 1.4 week HC: 38.8 ± 1.2 week (Mean ± SD, all *p* = NS)	– Postprandial glucose fell on both diets; Greater breakfast decrement on LC – Postprandial glucose lower on HC, no stats – 2 on LC and 1 on HC needed insulin
Moses et al. [71] Australia	RCT *N* = 63 31 LGI 32 HGI LGI: 32.0 ± 1.2 HGI: 32.8 ± 1.4	Need for insulin therapy Not powered	LGI: 37/33/24 26 g fiber GI = 48 HGI: 38/34/24 23 g fiber GI = 56	8–10 week* Begin 29.9–30.3 ± 0.2 week *GA not reported; exposure based on 40 week gestation	– 7d food records x2 – Achieved modest difference in GI targets	LGI: 29% required insulin HGI: 59% required insulin GWG not reported; stated not different	*LGA* LGI: 3 women HGI:3 women (*p* = NS) GA not reported	LGI: Less women required insulin – 50% of those on HGI who failed diet avoided insulin by switching to LGI diet – High insulin frequency on both

(continued)

Table 33.4 (continued)

Study	Design/*N* Maternal BMI[a] (kg/m^2)	Primary outcome Power	Intervention	Exposure length	Compliance	Maternal outcome[b]	Infant outcome[b]	Conclusion/Comment
Louie et al. [58] Australia	RCT *N* = 92 47 LGI 45 Fiber 50% Asian LGI: 23.9 ± 4.4 Fiber: 24.1 ± 5.7 Pre-pregnancy	Difference in infant BW between groups Powered on 260 g difference	LGI: 39/35/24 27 g fiber GI = 47 Fiber: 40/35/22 25 g fiber GI = 53	6–7 week Begin 29–29.7 ± 3.5–4.0 week	– 3d food records 36–37 week – 3 visits with RD; 24-h recall – Sample food baskets provided	– 53.2% on LGI versus 65.1% on Fiber required insulin ($p > 0.05$) – GI similar between diets ($p > 0.05$) *Total GWG* LGI: 11.9 ± 0.7 kg Fiber: 13.1 ± 0.9 kg *Excessive GWG* LGI: 25% Fiber: 42% ($p = 0.095$)	*BW* LGI: 3.3 ± 0.1 kg at 39.1 week Fiber: 3.3 ± 0.1 kg at 39.2 week *LGA* LGI: 12.8% Fiber: 4.4% (Mean ± SEM; all p = NS)	– Trial stopped early; lack of power in BW outcome/smaller effect size (with 60/group, 260 g difference in BW estimated) – Women did not reach GI targets – High insulin frequency in both – 68% of sample with BMI < 25 kg/m^2 – More in Fiber gained excessive GWG (p = NS)
Louie et al. [72] Australia 3-mo follow-up to 2011 study [58]	RCT *N* = 58 of 99 randomized 33 LGI 25 Fiber 60% Asian Maternal BMI as above	Secondary outcomes from above Powered on primary outcome described above	As above	As above	– 43 of 58 subjects (74%) were compliant by above methods	*BMI* LGI: 25.8 (range 24.2–27.3) Fiber: 26.3 (24.5–28.2) ($p > 0.05$) – 55% on LGI versus 60% on Fiber required insulin ($p > 0.05$) – Fasting glucose, post-75 g OGTT glucose at 3 mos similar ($p > 0.05$); 73% NGT LGI, 76% NGT Fiber – Weight loss, lipids similar	No differences: – Weight for age percentile – Length for age percentile – Weight for length percentile – Weight gain (g/d) Adjusted for breastfeeding status	No difference: – Postpartum maternal measures – Infant growth measures or growth patterns – Secondary outcomes; could be underpowered – Original trial was also stopped early as above
Asemi et al. [62] Iran	RCT *N* = 34 17 DASH 17 CON DASH 29.0 ± 3.2 CON 31.8 ± 5.9	Glucose tolerance, lipid profiles Powered on difference in HDL between groups	DASH: 67/18/17 Fiber 23 g Sodium: 1379 mg SFA 19% Added sugar 9 g CON: 54/29/18 Fiber 16 g Sodium 3859 mg SFA 26% Added Sugar 20 g	4 week Begin 24–28 week	– 3d food records – Phone follow-up – 7d menus provided Compliance not rated	DASH: – Improved response OGTT – Lower A1c, TC, LDL – Decreased SBP – Lower C/S rate – 12% on DASH and 59% on CON needed insulin AFTER delivery *GWG while in study* – ~1 kg both groups; $p > 0.05$	*BW* DASH: 3083 ± 402 CON: 3641 ± 579 (Mean ± SD) GA not reported	– DASH had lower SFA, added sugar, more fiber – No reasons for C/S noted – No urine sodium – High requirement for insulin after delivery – Diet intervention was 4 week—dietary intake through delivery not reported

(continued)

Table 33.4 (continued)

Study	Design/*N* Maternal BMI[a] (kg/m^2)	Primary outcome Power	Intervention	Exposure length	Compliance	Maternal outcome[b]	Infant outcome[b]	Conclusion/Comment
Asemi et al. [63] Iran Duplicate publication of above study based study number	RCT *N* = 32 16 DASH 16 CON DASH 30.8 ± 4.6 CON 29.7 ± 3.3	Insulin resistance, serum hsCRP, oxidative stress markers Powered on difference in hsCRP between groups	DASH: 65/18/18 Fiber 23 g Sodium 1394 mg SFA 20% Added Sugar 9 g CON: 53/28/18 Fiber 16 g Sodium 3883 mg SFA 28% Added Sugar 20 g DASH is designed to emphasize LGI foods and higher micronutrient intake	4 week Begin 24–28 week	– 3d food records – Phone follow-up – 7d menus provided Compliance not rated	DASH: – Decreased FBG, improved fasting insulin – Improved HOMA-IR – Increased total antioxidant capacity – Increased total glutathione CON: – Decreased total antioxidant capacity – Decreased total glutathione – Women requiring insulin not reported (compare to above) – No change in hsCRP *GWG while in study* – ~2 kg both groups; $p > 0.05$	–	– **Duplicate data from above with discrepancies in reporting**, including different primary outcomes/power analyses, maternal BMI DASH: – More arginine and antioxidant rich foods – Improved insulin resistance (fasting conditions only) – Improved antioxidant capacity – Diet intervention was 4 week—dietary intake through delivery not reported
Asemi et al. [64] Iran	RCT *N* = 58 29 DASH 29 CON DASH 29.2 ± 3.5 CON 31.0 ± 4.9	Infant BW between groups Powered on a difference of 75 g in BW between groups	DASH: 66/18/17 Fiber 23 g Sodium 1429 mg SFA 20% Added Sugar 13 g CON: 54/28/18 Fiber 16 g Sodium 3821 mg SFA 27% Added Sugar 22 g	4 week Began 26 ± 1 week After intervention, 3 from each group had a medical exclusion	– 3d food records – Phone follow-up Compliance not rated	*C/S* DASH: 46.2% CON: 81% *Needed insulin after intervention* DASH: 23% CON: 73% *GWG while in study* – ~2 kg both groups; $p > 0.05$	*Macrosomia* DASH: 3.8% CON: 39% *BW* DASH: 3223 ± 97 g CON: 3819 ± 97 g Ponderal index, head circumference lower in DASH *GA* DASH: 38.4 ± 1.2 week CON: 38.2 ± 1.2 week ($p > 0.05$)	– Background prevalence of C/S outside of GDM is 47–84% in Iran; 90% in GDM – Need for insulin might be attributable to diet intake after the intervention, which is not accounted for – Powered on a 75 g between-group difference in BW (21/group needed), plus showed significant maternal/infant outcomes. Louie et al. [58] did not detect a difference in BW with a larger sample size

(continued)

Table 33.4 (continued)

Study	Design/*N* Maternal BMI[a] (kg/m^2)	Primary outcome Power	Intervention	Exposure length	Compliance	Maternal outcome[b]	Infant outcome[b]	Conclusion/Comment
Moreno-Castilla et al. [61] Spain	RCT *N* = 150 75 LC 75 CON LC 25.4 ± 5.7 CON 26.6 ± 5.5 Pre-pregnancy	Risk for need of insulin therapy Powered on 22% difference in need for insulin rate between groups	LC: ~40/40/20 *CHO: 177.1, 187.5 g/d *Sugars: 82.1, 84.2 g/d *Starches: 90.7, 99.1 g/d CON: ~55/25/20 *CHO: 202.7, 236.7 g/d *Sugars: 75.6, 81.7 g/d *Starches: 123.4, 142.5 g/d *Actual: start, during diet	6–12 week based on GA 39 week Begin 30 ± 3 week	– Diet records near study start and during study; exact timing unclear – Assessed CHO, sugars, and starches only – 90–91% returned records at start; 63–67% during diet – Both groups under-consumed CHO (start); only LC group met target during diet	*Total GWG* CON: 2.3 ± 2.3 kg LC: 1.4 ± 2.0 kg – 54.7% of women in each group required insulin – No difference in time to insulin, insulin dose – Similar maternal outcomes	*SGA* LC: 10.8% CON: 16.0% *LGA* LC: 4.1% CON: 8.0 *Macrosomia* LC: 1.4% CON: 6.7% *GA* LC: 39.0 ± 2.1 week CON: 38.9 ± 1.8 week (all $p > 0.05$)	– 20% drop-out rate on CON versus 7% LC – Noncompliance in both groups – Total energy, protein, fat intake not reported – Sugar intake was constant. Reduced CHO in both groups accounted for by decreased starch intake – Total GWG was greater in CON; more dropouts, unclear compliance – No difference in need for insulin therapy/time to insulin therapy – Wide range in exposure time
Hu et al. [55] China	RCT *N* = 140 66 LGI 74 CON LGI 21.2 ± 2.5 CON 20.9 ± 3.4 Pre-pregnancy	Postprandial glucose response Not powered	LGI: white rice replaced with LGI staple food, lunch/dinner CON: white rice was staple food, lunch dinner LGI staple and control staple (rice) matched by CHO content (g) and energy Breakfast same between groups	4 days LGI 27.0 ± 2.7 week CON 27.9 ± 3.8 week (p = NS)	Hospitalized Day 1 baseline Diet began on day 2 Foods provided	LGI/CON: – Both showed lower PP glucose across meals LGI: – Decreased FBG, greater decrement in 2-h PP glucose across meals versus CON – PP glucose lower versus CON across meals CON: – No difference in FBG	–	– Replacement of HGI rice with LGI staple (brown rice) improved FBG and PP glucose – Decrement range on LGI was – 3.7 ± 7.6% (FBG) and – 19 to 22 ± 12–14% (PP) Compared to CON – 1.2 ± 6.8% (FBG) and – 7 to 12 ± 8–18% (PP) (mean ± SD) – BMI at week of study not reported
Hernandez et al. [56] United States	Randomized crossover *N* = 16 33.6 ± 1.1	24 h glucose area-under-the-curve (AUC) by continuous glucose monitoring Powered on difference in glucose AUC within women between groups	LC: 40/45/15 Fiber 23.5 g HC: 60/25/15 Fiber 29.3 g – Matched for fatty acids (MUFA/PUFA/SFA) – Simple Sugars ≤ 18% of total calories	3d each Begin 31.2 ± 0.5 week 2d lead-in/2.5d washout diet in between Breakfast test meal (30% of total calories) on last day of each diet	– 100% of calories provided – Meals picked up every 72 h – In-person contact with women 5 times over 12-day protocol, plus frequent phone contact	Both diets: – Glycemia controlled to below targets – Mean 24-h and nocturnal glucose similar within women between diets HC: Total glucose AUC 6% higher versus LC – Daytime mean glucose 98 ± 2 mg/dL	–	– HC diet included more complex CHO – Both LC and HC diets controlled glycemia; CHO restriction may not be required – 6% higher glucose over 24 h on HC – 19% higher post-breakfast lipemia on LC – GI: low to moderate on both diets – All GDM was diet-controlled without medication

(continued)

Table 33.4 (continued)

Study	Design/*N* Maternal BMI[a] (kg/m^2)	Primary outcome Power	Intervention	Exposure length	Compliance	Maternal outcome[b]	Infant outcome[b]	Conclusion/Comment
			– Calorie distribution Breakfast: 25% Lunch: 25% Dinner: 30% Snacks: 20% Continuous glucose monitors during diets			LC: After breakfast, FFA AUC 19% higher than HCC – Daytime mean glucose 93 ± 3 mg/dL		
Hernandez et al. [57] United States Follow-up to crossover study [56]	RCT *N* = 12 6 LC 6 HCC LC 33.4 ± 1.4 HC 34.3 ± 1.6	Secondary outcomes from above Powered on primary outcome described above	LC: 40/45/15 Fiber 23.5 g HC: 60/25/15 Fiber 29.3 g See above Fasting blood/adipose tissue harvest at 37 week	6–7 weeks Women stayed on second diet from crossover through delivery	– Meals provided (details above)	LC: – 31% suppression of adipose tissue lipolysis – Increase in FBG from 31 to 37 week HC: – 56% suppression of adipose tissue lipolysis versus LC – Decrement in FBG from 31 to 37 weeks Across women: – Maternal fasting plasma insulin and HOMA-IR (37 week) were correlated with infant adiposity (r = 0.697, r = 0.731) *GWG while in study* LC: 1.7 ± 1.6 kg HCC: 2.3 ± 1.2 kg ($p > 0.05$)	*BW* LC: 3421 ± 186 g HC: 3273 ± 104 g *GA* LC: 39.2 ± 0.4 week HC: 40.5 ± 0.5 week *2 week Infant % Adiposity* LC: 12.6 ± 2.0% HC: 10.1 ± 1.4% – Similar weight, lean mass	– 3 Hispanic women in LC – Better suppression of lipolysis on HC diet suggests improved insulin resistance on background of pregnancy-induced insulin resistance – Improved FBG supports improved insulin resistance – Secondary outcomes; could be underpowered on some measures – All GDM was diet-controlled without medication – Correlations between maternal markers of insulin resistance and infant %adiposity suggest adipose tissue insulin action as a target for diet therapy

Trials are listed in chronological order by publication date. Shaded rows indicate follow-up from a preceding publication

Macronutrients are (Carbohydrate/Fat/Pro). Percent distributions are as reported and may not total 100%. *HC* High carbohydrate; *LC* Low carbohydrate; *CHO* Carbohydrate; *TC* Serum total cholesterol; *FFA* Free fatty acids; *OGTT* Oral glucose tolerance test; *ADA* American Diabetes Association Diet; *SMBG* Self-monitored blood glucose; *GWG* Gestational weight gain; *BW* Infant birth weight; *LGI/HGI* Low or high-glycemic index; *LGA* Large-for-gestational-age/infant birth weight ≥90th centile; *NGT* Normal glucose tolerance; *DASH* Dietary approaches to stop hypertension diet; *CON* Control; *SFA* Saturated fatty acids; *LDL* Low-density lipoprotein cholesterol; *C/S* Cesarean section; *hsCRP* Highly sensitive C-reactive protein; *FBG* Fasting blood glucose; *HOMA-IR* Homeostatic model for insulin resistance; *SGA* Small-for-gestational-age/infant birth weight ≤10th centile; *PP* Postprandial; *MUFA* Monounsaturated fatty acids; *PUFA* Polyunsaturated fatty acids

[a]BMI at time of intervention start, unless specified

[b]All differences are $p < 0.05$ unless specified

In fact, the U.S. group provided all food for 6–7 weeks through delivery [57] and showed that women who consumed the liberalized complex carbohydrate diet (60% of total calories) had a *decrease* in fasting glucose while those on the lower carbohydrate (40% of total calories) diet manifested *increased* fasting glucose. It is also important to underscore that in these trials where complex carbohydrates were liberalized, protein ranged 15–20%, and total fat content was lower (10–25%) with lower saturated fat. The lower total fat content, particularly lower saturated fat, could have added to the beneficial effects on glucose metabolism due to reduced FFA-induced worsening of insulin resistance [68] and enhanced insulin signaling effects [69]. Overall, despite the limitations of each study (Table 33.4), the evidence supports that women with GDM tolerate liberalization of higher quality complex carbohydrates compared to lower carbohydrate exposures, and are able to achieve good glycemic control.

Higher Carbohydrate Diets: Metabolic Effects beyond Maternal Glucose. Evidence from the trials (Table 33.4) suggests that a balanced liberalization of complex carbohydrates portends benefits to maternal metabolism beyond glucose control. For example, in the short-exposure crossover studies, the higher complex carbohydrate diets demonstrated lower fasting total cholesterol, lower fasting FFA (70% carbohydrate/10% fat) [54], and a lower postprandial FFA area-under-the-curve in response to a controlled meal tolerance test (60% carbohydrate/25% fat) [56]. Moreover, Persian women who consumed the DASH low-sodium diet (65–67% carbohydrate/18% fat) for 4 weeks beginning in gestational week 24–28 demonstrated lower hemoglobin A1C, total cholesterol and low-density lipoprotein cholesterol, and systolic blood pressure [62], as well as an improved insulin resistance index (HOMA-IR) [63]. Interestingly, the study in Persian women further suggested that the DASH diet resulted in increased total glutathione and antioxidant capacities, while the control group (53% carbohydrate/28% fat) demonstrated decreased levels [63]. The suggestion of increased antioxidant activity could be attributable to the DASH diet being high in nutrient-dense, higher quality complex carbohydrates that contain more vitamins and minerals. In the U.S., where all food was provided through delivery [57], studies in harvested adipose tissue biopsies revealed a nearly doubled suppression of isoproterenol-stimulated lipolysis (56% suppression) in those following the higher complex carbohydrate diet (60% carbohydrate/25% fat) compared to those following the lower carbohydrate diet (31% suppression; 40% carbohydrate/45% fat). These findings suggest better adipose tissue insulin action with the higher complex carbohydrate exposure after 6–7 weeks. Taken together, these studies suggest that liberalization of higher quality complex carbohydrates in combination with lower total/saturated fat resulted in improved insulin action and lipemia despite the heightened insulin resistance of pregnancy. Further, there are suggestions of potential vascular benefits due to higher antioxidant capacity and lower blood pressure, both of which may be linked to increased intakes of nutrient-dense complex carbohydrates that contain more vitamins/minerals, and lower sodium.

Need for Insulin Therapy. An unbalanced increase in total carbohydrates, particularly those known to acutely raise blood glucose, undoubtedly increases risk for insulin therapy. Historically, it was demonstrated in nonrandomized studies that glycemic control could be achieved using diet + insulin [4], but that women who consumed <42% carbohydrate could avoid insulin therapy (vs. 42–50% carbohydrate) [70]. Fortunately, two of the trials listed in Table 33.4 addressed the need for insulin therapy in relation to diet using randomized study designs. In Australia, Moses et al. [71] demonstrated that less women (29%) randomized to a low-GI diet required insulin therapy (vs. higher-GI, 59% needed insulin; GI: 48 vs. 56, respectively). Moreover, 50% of women who failed to maintain acceptable glycemia with a higher-GI diet were able to avoid insulin therapy by switching to a low-GI diet. It is important to note that fiber was similar in the low- and high-GI groups (26 g low-GI vs. 23 g higher-GI), and that both exposures contained low- to moderate-GI foods (Table 33.2). In Spain, Moreno-Castilla et al. [61] implemented a RCT powered on the risk for needing insulin therapy. 54.7% of women randomized to both low-carbohydrate (~40% carbohydrate/40% fat) and control exposures (~55% carbohydrate/25% fat) required insulin,

making the finding negative. Unfortunately reported intakes of total energy, fat and protein were not reported. However, close inspection of the total carbohydrate, sugar, and starch intakes reveal important patterns that help interpret the negative finding. First, in women on the low-carbohydrate diet, simple sugars represented more proportion of total carbohydrates than the control group. In the low-carbohydrate group, 44% of total carbohydrate intake was simple sugars, while starches represented 52%. In the control group, simple sugars represented 35% of total carbohydrate and starches represented 60% of total carbohydrate intake. Importantly, neither group decreased their simple sugars over the 6–12 week intervention. The control group actually had a higher intake of starches/complex carbohydrates as a percentage of total calories (60% vs. 52% in low-carbohydrate), but the drop-out rate was 20% (vs. 7%), which could have obscured the ability to see other benefits on glucose metabolism and insulin action as previously described. It is interesting to note that in Persian women with GDM, fewer women randomized to a DASH diet for 4 weeks beginning in gestational week 24–28 (66% carbohydrate/18% fat vs. 54% carbohydrate/28% fat) required insulin during the last trimester of pregnancy after the intervention ended (23% vs. 73% in control group). It is possible that 4 weeks of exposure to a greater percentage of higher quality complex carbohydrates imparted benefits on insulin action, vascular function, etc., that were able to last after the intervention stopped through delivery, helping women avoid insulin therapy. On the other hand, actual dietary consumption is unknown in the last trimester, and this could explain the need for insulin in women who required it. Overall, the data support that a balanced liberalization of higher quality complex carbohydrates, in which GI and simple sugars are lower, can potentially reduce the need for insulin therapy in GDM.

Higher Carbohydrate Diets and Maternal/Infant Outcomes. Very few trials of nutrition therapy in GDM included infant outcomes, but two trials (Table 33.4) were powered on a difference in infant birth weight. In Australia, Louie et al. [58] executed a RCT to compare the impact of a low-GI (GI 47/37% carbohydrate/33% fat/27 g fiber) to a higher-GI diet (GI 53/40% carbohydrate/35% fat/25 g fiber) on infant birth weight (powered on 260 g difference). Unfortunately, women were unable to meet the GI targets, and thus the GI, fiber, and macronutrient distribution were similar between groups. The trial was stopped early due to a lack of power to detect a difference in infant birth weight. It is important to note that 50% of this sample contained Asian women with a lower BMI, who often manifest postprandial instead of fasting hyperglycemia [1], introducing significant ethnic heterogeneity. Also, the need for insulin therapy was high in both diet groups (53% in low-GI; 65% in higher-GI). The lack of differences might be attributable to the similarity of the diet exposures in GI (6 GI points difference) and macronutrient distribution, and the 50% proportion of Asian women in the sample. In a 3-month follow-up to this study (58% of the original mothers and their offspring, of whom 60% were Asian) [72], no differences were seen on parameters of postpartum maternal glucose metabolism or postpartum weight loss, nor were differences in infant growth patterns seen. In Persian women [64] (DASH vs. control, 4-week exposure, Table 33.4), the primary outcome of infant birth weight was powered on a 75 g difference between groups. In contrast to the Australian group [58], these investigators surprisingly reported that women randomized to DASH (during gestational weeks 26–31 only) demonstrated a lower infant birth weight (3223 g vs. 3819 g control; similar gestational age), as well as rate of cesarean section (46.2% vs. 81% control), macrosomia rate (3.8% vs. 39% control), ponderal index and head circumference. In the Persian women [64], the diet exposures were markedly different between DASH and control within a more homogeneous sample of women; the high rate of cesarean delivery in both groups and fetal macrosomia in controls are certainly of interest. The DASH low-sodium diet, also low in fat, could have imparted benefits on insulin action and thus mitigated nutrient delivery to the fetus, resulting in lower birth weight and macrosomia incidence. This concept was supported by the U.S. group [57], who showed evidence for improved maternal insulin action and a trend for lower infant adiposity in women who followed a higher complex carbohydrate, lower fat diet for 6–7 weeks through delivery.

Fiber and Glycemic Index in Nutrition Therapy for GDM. When considering an approach to nutrition therapy for GDM that includes a balanced liberalization of higher quality complex carbohydrates, both fiber and GI become important factors as they are a component and a property, respectively, of carbohydrate foods.

Fiber in GDM. Only one RCT (Table 33.4) formally compared a high-fiber diet (80 g fiber/ 60% carbohydrate/20% fat) to one with lower fiber (20 g fiber/50% carbohydrate/30% fat) in women with GDM. Women self-monitored their glucose 6 times/day only 2 days/week, which greatly differs from current and past standard of care [65]. Also, total carbohydrate was not constant in both groups. There was no difference in glycemic control between high- and low-fiber exposures from the limited glucometer records. Compliance was marginal (40–60%) and the drop-out rate was unclear. To reach the 80 g fiber goal in the intervention group required use of a supplement on top of increasing intake of high-fiber foods. Women had trouble tolerating the fiber, reporting diarrhea, excess flatulence, and nausea/vomiting. In the crossover study of Nolan [54] fiber intolerance was also reported (70 g fiber/70% carbohydrate vs. 31 g fiber/35% carbohydrate), but the improvements in glycemic control over 4 days could in part be explained by fiber. As previously described, recent studies have demonstrated that fiber content has little or no association with postprandial glycemia or insulinemia [49]. Instead of fiber, these studies outside of pregnancy [49] have shown that glycemic load (global insulin demand) is the most potent predictor of glycemic response to single foods, explaining 85% of the variance, while total carbohydrate content explained 58%. In mixed meals, glycemic load remained the most potent predictor of glycemic response, but accounted for less of the variance (58%) [15, 50]. Across the remainder of studies in GDM (Table 33.4), the difference in fiber between higher and lower carbohydrate exposures was modest (2–7 g), making it unlikely to have explained improvements in glucose tolerance. It is important to note, however, that higher quality complex carbohydrates tend to have higher fiber content if they are from vegetable, legume, or whole grain sources. Benefits of higher fiber diets have been linked to lower cancer, diabetes and CVD risk [13, 73], and have been associated with bioactivity of some carbohydrate components (i.e., plant sterols) [73], increased micronutrient content, antioxidant content, or in differences in colonic fermentation [49].

Glycemic Index in GDM. The studies in which a low-GI versus high-GI diet exposure was compared (Table 33.4) resulted in less need for maternal insulin therapy [71], but no difference in infant birthweight [58], postpartum maternal glucose parameters, or infant growth patterns [72]. Nonetheless, Hu [55] conducted a carefully controlled RCT in China, where high-glycemic rice is a staple food consumed throughout the day. Asian women with GDM (BMI 20–21 kg/m^2) were admitted to a metabolic ward where all food was provided, and were randomized to 4-days of either replacement of rice with a low-GI staple food (brown rice) versus control (white rice was maintained as the staple food) (total carbohydrate/energy content held constant). While both groups demonstrated lower postprandial glucose across meals, likely due to calorie control, women in the low-GI staple group had decreased fasting glucose (−3.7% vs. −1.2%, respectively) and a greater reduction in postprandial glucose (−19 to −22% vs. −7 to −12%, respectively). It might be that in the larger free-living studies in Australia [58, 72], a narrow difference in GI alone in the setting of similar overall macronutrient compositions between diet exposures obscured the ability to see differences in some maternal and infant outcomes, such as infant birth weight/growth patterns.

Glycemic Index outside of GDM Pregnancies. Outside of pregnancy and in non-GDM pregnancies, there is mounting evidence supporting the use of low-GI/low-GL diets (Table 33.2) to encourage consumption of higher quality "healthier" carbohydrates for control of postprandial glycemia in obesity and impaired glucose tolerance [13]. For example, in mixed mothers with GDM/impaired glucose tolerance, a low-GI (vs. high-GI) diet was shown to result in more postprandial glucose values in the target range for control, but no overall significant difference in glycemia between groups [74]. The RCT of Walsh [75] included 800 women at risk for fetal macrosomia. Women were randomized to a low-GI versus high-GI diet. Although no significant difference was found on infant birth weight, women on the low-GI diet had lower gestational weight

gain by 1.5 kg and less incidence of a higher fasting glucose (>92 mg/dL) or a 50 g glucose challenge >140 mg/dL [76]. Thus, low-GI diets may be an effective strategy for preventing excessive gestational weight gain. In women *at risk for GDM*, low-GI diets have not resulted in a difference in pregnancy outcomes [77], although a self-selected subgroup analysis revealed that in women who followed a low-GI diet (GI:51 vs. high-GI, GI:57), the *offspring* had lower birthweight/length z-scores with evidence of lower aortic intima-medial thickness at 12 months of life [78]. According to the ranges in Table 33.2, both of the diet exposures were actually low- and moderate-GI. Although a subgroup analysis, lower aortic intima-medial thickness supports the earlier mentioned vascular impacts observed in GDM with exposure to the DASH diet, which imparted evidence of greater antioxidant activity.

The evidence as a whole supports implications that low-GI diets impart improvements in postprandial glucose, insulin action, and vascular health, as well as in mitigation of excessive gestational weight gain. These benefits may be linked to increased consumption of higher quality complex carbohydrates, which overall are lower in GI, more nutrient dense [79] and have been linked with greater satiety [13].

Higher Carbohydrate Diets and Gestational Weight Gain. It has been suggested that a diet containing 50–60% carbohydrate often leads to excessive weight gain and postprandial hyperglycemia, which fuels the focus on rigid restriction of carbohydrate in women with GDM [80]. Indeed, a chronically high consumption of high-GI foods in combination with a high-glycemic load has been implicated in the evolution of type 2 diabetes and cardiovascular disease [13]. Weight gain might be expected in the setting of caloric excess and high consumption of refined carbohydrates that acutely increase blood glucose, where higher insulinemia would promote more lipid storage due to increased adipose tissue lipoprotein lipase activity [43]. The RCTs in Table 33.4 represent a BMI range of 25–34 kg/m^2 outside of Asian women. In Spain [61], women in the control group (55% carbohydrate/25% fat) gained significantly more weight (2.3 kg) versus those in low-carbohydrate (40% carbohydrate/40% fat), who gained 1.4 kg. However, it must be emphasized that only *total gestational weight gain* was reported; thus, it is possible that the women in the control group gained more weight before the intervention began at 30 weeks. In Australia, Louie et al. [58] also reported that 42% of those in the higher GI control group had excessive gestational weight gain [41], compared to only 25% of women randomized to the low-GI diet. Again, it must be underscored that only *total gestational weight gain* was reported; weight gained before the intervention began at 25–34 weeks is unknown. The higher proportion of insulin therapy in both groups could also confound the gestational weight gain finding, since insulin therapy is associated with weight gain.

Three trials (Table 33.4) reported weight gained *during the diet intervention* [57, 62–64], which was ~1–2 kg during either higher or lower carbohydrate exposure. Across the remainder of trials, given the limitation in reporting of gestational weight gain, weight gain does not appear to overtly confound any of the outcomes reported in women with a BMI between 25 and 34 kg/m^2. Moreover, as previously discussed, the studies of low-GI diets outside of GDM support reduced excessive gestational weight gain due to less energy intake [76], probably linked to increased satiety [13]. More research is warranted in women with GDM who have a BMI > 35 kg/m^2, in which added co-morbidities occur and an overall higher calorie consumption is required (thus higher carbohydrate, fat and protein portions) to prevent weight loss and potential maternal ketosis. Nevertheless, at least when calories are not in excess, the evidence supports that a balanced liberalization of higher quality complex carbohydrates results in appropriate gestational weight gain.

Recommendations

Nutrition therapy is the single treatment component that will reach every woman with GDM independent of diagnostic criteria. Despite the adaptive insulin resistance of pregnancy, an optimal mixture of higher quality complex carbohydrates with less glycemic potential, lower fat, and appropriate protein in the context of higher overall diet quality holds potential for promotion of good glycemic health while meeting pregnancy nutritional goals. An approach to nutrition therapy in GDM that includes a balanced liberalization of higher quality complex carbohydrates in the context of flexible eating restraint could help mitigate anxiety and avoid unintended consequences associated with compensatory higher fat intake. Evidence from 10 RCTs in which type or amount of dietary carbohydrate was manipulated was critically reviewed. Major limitations of studies included dietary noncompliance, confounding insulin therapy, inconsistent reporting of BMI (pre-pregnancy, intervention baseline), and inconsistent reporting of gestational weight gain (total, during intervention). It is also important to note that only 50% of the women represented participated in an adequately powered trial. Nonetheless, the preponderance of evidence in GDM (Table 33.5) suggests that a balanced liberalization of higher quality complex carbohydrates results in good maternal glycemic control, improved lipemia, vascular benefits, improved insulin action, and improved glucose tolerance despite the background of pregnancy-induced insulin resistance. Low-GI diets may reduce the need for insulin, and lessen postprandial hyperglycemia. Future prospective randomized trials are suggested to include: Increased use of controlled studies where food is provided; a priori determination of a primary outcome with adequate power analysis; consistent reporting of pre-pregnancy BMI/BMI at time of intervention, as well as total gestational weight gain and weight gained during intervention; inclusion of maternal/infant outcomes, particularly infant adiposity; control of confounders such as additive medication, dissimilar energy intake between exposures; improved approaches to dietary adherence; homogeneous samples of women in terms of ethnicity, glucose metabolism [65]; reporting of both the glucose management target and achieved glycemia [65]; and increased reporting of types of foods consumed.

Table 33.5 Evidence-based summary of potential benefits to a balanced liberalization of higher quality complex carbohydrates in nutrition therapy for GDM

Potential benefits: overall balanced liberalization of higher quality carbohydrates
– Overall improved maternal glucose control to equal or superior levels of carbohydrate restriction
– Improved response to oral glucose tolerance test
– Improved fasting glucose
– Decreased: serum total cholesterol, low-density lipoprotein cholesterol
– Decreased: fasting and postprandial lipemia (free fatty acids)
– Improved A1c
– Improved insulin action, insulin resistance index, systolic blood pressure
– Increased total glutathione/antioxidant capacity
– Appropriate gestational weight gain when calories are not in excess
– Improved maternal outcomes (less cesarean delivery)
– Improved infant outcomes (less macrosomia, less birth weight)
Potential benefits: low-gi carbohydrate diets
– Less need for insulin therapy
– Improved postprandial glucose (controlled meals)

When carbohydrates are liberalized, the macronutrient mixture tends to also include lower fat and moderate protein intake. An approach that includes flexible eating restraint instead of rigid control may help mitigate diagnosis-associated anxiety and facilitate nutrition therapy success

Conclusions

Identifying a diet for GDM that can alter maternal/fetal metabolism in late pregnancy when fetal growth accelerates is critical to reducing short- and long-term metabolic risk in this growing cohort of mothers and infants. Nutrition therapy in GDM holds great potential to effectively treat this population by optimizing the intrauterine environment. Mounting evidence herein reviewed supports that a balanced liberalization of higher quality complex carbohydrates may be part of an effective approach to nutrition therapy in GDM that could provide the foundation for a lifetime higher diet quality in mother and offspring.

References

1. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care. 2012;35(3):526–8.
2. Hernandez TL, Anderson MA, Chartier-Logan C, Friedman JE, Barbour LA. Strategies in the nutritional management of gestational diabetes. Clin Obstet Gynecol. 2013;56(4):803–15.
3. Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. Clin Obstet Gynecol. 2013;56(3):511–9.
4. Mestman JH. Historical notes on diabetes and pregnancy. Endocrinol. 2002;12:224–42.
5. Jovanovic-Peterson L, Peterson CM. Dietary manipulation as a primary treatment strategy for pregnancies complicated by diabetes. J Am Coll Nutr. 1990;9(4):320–5.
6. Hernandez TL. Nutrition therapy in gestational diabetes: the case for complex carbohydrates. Diabetes Spectr. 2016;29(2):82–8.
7. Westman EC, Yancy WS Jr, Humphreys M. Dietary treatment of diabetes mellitus in the pre-insulin era (1914–1922). Perspect Biol Med. 2006;49(1):77–83.
8. Metzger BE, Buchanan TA, Coustan D, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on Gestational Diabetes Mellitus. Diabetes Care. 2007;30(Suppl 2):S251–60.
9. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. Cochrane Database Syst Rev. 2013;3:CD009275.
10. Barrett HL, Dekker NM, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? Diabetes Care. 2014;37(5):1484–93.
11. Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care. 2008;31(9):1858–63.
12. Wolever TM. Is glycaemic index (GI) a valid measure of carbohydrate quality? Eur J Clin Nutr. 2013;67(5):522–31.
13. Augustin LS, Kendall CW, Jenkins DJ, Willett WC, Astrup A, Barclay AW, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). Nutr Metab Cardiovasc Dis. 2015;25(9):795–815.
14. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary guidelines for Americans. 2015. Report No.: 8th ed.
15. Small P, Brand-Miller JC. From complex carbohydrate to glycemic index: tracing the controversy. Nutr Today. 2009;44(6):236–43.
16. Freinkel N. Banting lecture 1980. Of pregnancy and progeny. Diabetes. 1980;29(12):1023–35.
17. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Del Prato S. Intermediate metabolism in normal pregnancy and in gestational diabetes. Diabetes Metab Res Rev. 2003;19(4):259–70.
18. Buchanan TA, Xiang A, Kjos SL, Watanabe RM. What is gestational diabetes. Diabetes Care. 2007;30(Suppl 2):S105–11.
19. Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000;71(5 Suppl):1256S–61S.
20. Sivan E, Chen X, Homko CJ, Reece EA, Boden G. Longitudinal study of carbohydrate metabolism in healthy obese pregnant women. Diabetes Care. 1997;20(9):1470–5.
21. Sivan E, Homko CJ, Whittaker PG, Reece EA, Chen X, Boden G. Free fatty acids and insulin resistance during pregnancy. J Clin Endocrinol Metab. 1998;83(7):2338–42.

22. Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. Clin Obstet Gynecol. 2007;50(4):972–9.
23. Lauenborg J, Hansen T, Jensen DM, Vestergaard H, Molsted-Pedersen L, Hornnes P, et al. Increasing incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. Diabetes Care. 2004;27(5): 1194–9.
24. Rogers I. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord. 2003;27(7):755–77.
25. Vohr BR, McGarvey ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. Diabetes Care. 1999;22(8):1284–91.
26. Catalano PM, Thomas A, Huston-Presley L, Amini SB. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. Am J Obstet Gynecol. 2003;189(6):1698–704.
27. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to fetal hyperinsulinism. Diabetes Care. 1995;18(5):611–7.
28. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3):e290–6.
29. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D'Agostino RB Jr, Liese AD, Vehik KS, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care. 2008;31(7):1422–6.
30. Wells JC, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. Proc Nutr Soc. 2007;66(3):423–34.
31. Ahlsson F, Gustafsson J, Tuvemo T, Lundgren M. Females born large for gestational age have a doubled risk of giving birth to large for gestational age infants. Acta Paediatr. 2007;96(3):358–62.
32. Barbour LA. Changing perspectives in pre-existing diabetes and obesity in pregnancy: maternal and infant short- and long-term outcomes. Curr Opin Endocrinol Diabetes Obes. 2014;21(4):257–63.
33. Friedman JE. Obesity and gestational diabetes mellitus pathways for programming in mouse, monkey, and man-where do we go next? The 2014 Norbert Freinkel Award Lecture. Diabetes Care. 2015 Aug;38(8):1402–11.
34. Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, et al. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature. 2011;478(7367):110–3.
35. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453(7196):783–7.
36. Lawson EJ, Rajaram S. A transformed pregnancy: the psychosocial consequences of gestational diabetes. Sociol Health Illn. 1994;16(4):536–62.
37. Hui AL, Sevenhuysen G, Harvey D, Salamon E. Stress and anxiety in women with gestational diabetes during dietary management. Diabetes Educ. 2014;40(5):668–77.
38. Smith-Morris CM. Diagnostic controversy: gestational diabetes and the meaning of risk for pima Indian women. Med Anthropol. 2005;24(2):145–77.
39. Hui AL, Sevenhuysen G, Harvey D, Salamon E. Food choice decision-making by women with gestational diabetes. Can J Diabetes. 2014;38(1):26–31.
40. Teixeira PJ, Carraca EV, Marques MM, Rutter H, Oppert JM, De Bourdeaudhuij I, et al. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. BMC Med. 2015;13:84.
41. Institute of Medicine, National Research Council. Weight gain during pregnancy: Reexamining the guidelines. Committee to reexamine IOM pregnancy weight gain guidelines. National Academies Press, Washington, D.C.: Institute of Medicine and National Research Council of the National Academies; 2009.
42. Magee MS, Knopp RH, Benedetti TJ. Metabolic effects of 1200-kcal diet in obese pregnant women with gestational diabetes. Diabetes. 1990;39(2):234–40.
43. Frayn K. Metabolic regulation: a human perspective. 2nd ed. Oxford, UK: Blackwell Science; 2003.
44. Holme AM, Roland MC, Lorentzen B, Michelsen TM, Henriksen T. Placental glucose transfer: a human in vivo study. PLoS ONE. 2015;10(2):e0117084.
45. Simpson SJ, Raubenheimer D. Obesity: the protein leverage hypothesis. Obes Rev. 2005;6(2):133–42.
46. Hernandez TL, Sutherland JP, Wolfe P, Allian-Sauer M, Capell WH, Talley ND, et al. Lack of suppression of circulating free fatty acids and hypercholesterolemia during weight loss on a high-fat, low-carbohydrate diet. Am J Clin Nutr. 2010;91(3):578–85.
47. Gropper SS, Smith JL, Groff JL. Advanced nutrition and human metabolism. 4th ed. Belmont, CA, USA: Thomson Wadsworth; 2005.
48. Aziz A, Dumais L, Barber J. Health Canada's evaluation of the use of glycemic index claims on food labels. Am J Clin Nutr. 2013;98(2):269–74.
49. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011; 93(5):984–96.
50. Brand-Miller JC, Buyken AE. The glycemic index issue. Curr Opin Lipidol. 2012;23(1):62–7.

51. Moses RG, Brand-Miller JC. The use of a low glycaemic index diet in pregnancy: an evolving treatment paradigm. Diabetes Res Clin Pract. 2011;91(1):13–4.
52. International Organization for Standardization. Determination of glycaemic index and recommendation for food classification. International Organization for Standardization 2010(ISO 26642:2010). Available from: URL: https://www.iso.org/obp/ui/#iso:std:iso:26642:ed-1:v1:en.
53. Eckel RH. Role of glycemic index in the context of an overall heart-healthy diet. JAMA. 2014;312(23):2508–9.
54. Nolan CJ. Improved glucose tolerance in gestational diabetic women on a low fat, high unrefined carbohydrate diet. Aust N Z J Obstet Gynaecol. 1984;24(3):174–7.
55. Hu ZG, Tan RS, Jin D, Li W, Zhou XY. A low glycemic index staple diet reduces postprandial glucose values in Asian women with gestational diabetes mellitus. J Investig Med. 2014;62(8):975–9.
56. Hernandez TL, van Pelt RE, Anderson MA, Daniels LJ, West NA, Donahoo WT, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. Diabetes Care. 2014;37(5):1254–62.
57. Hernandez TL, van Pelt RE, Anderson MA, Reece MS, Reynolds RM, de la Houssaye BA, et al. Women With gestational diabetes mellitus randomized to a higher-complex carbohydrate/low-fat diet manifest lower adipose tissue insulin resistance, inflammation, glucose, and free fatty acids: a pilot study. Diabetes Care. 2016;39(1):39–42.
58. Louie JC, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, et al. A randomized controlled trial investigating the effects of a low-glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. Diabetes Care. 2011;34(11):2341–6.
59. Reece EA, Hagay Z, Gay LJ, O'Connor T, Degennaro N, Homko CJ, et al. A randomized clinical trial of a fiber-enriched diabetic diet vs. the standard American Diabetes Association-recommended diet in the management of diabetes mellitus in pregnancy. J Matern Fetal Invest. 1995;5:8–12.
60. Cypryk K, Kaminska P, Kosinski M, Pertynska-Marczewska M, Lewinski A. A comparison of the effectiveness, tolerability and safety of high and low carbohydrate diets in women with gestational diabetes. Endokrynol Pol. 2007;58(4):314–9.
61. Moreno-Castilla C, Hernandez M, Bergua M, Alvarez MC, Arce MA, Rodriguez K, et al. Low-carbohydrate diet for the treatment of gestational diabetes: a randomized controlled trial. Diabetes Care. 2013 Apr 5.
62. Asemi Z, Tabassi Z, Samimi M, Fahiminejad T, Esmaillzadeh A. Favourable effects of the dietary approaches to stop hypertension diet on glucose tolerance and lipid profiles in gestational diabetes: a randomised clinical trial. Br J Nutr. 2013;109(11):2024–30.
63. Asemi Z, Samimi M, Tabassi Z, Sabihi SS, Esmaillzadeh A. A randomized controlled clinical trial investigating the effect of DASH diet on insulin resistance, inflammation, and oxidative stress in gestational diabetes. Nutrition. 2013;29(4):619–24.
64. Asemi Z, Samimi M, Tabassi Z, Esmaillzadeh A. The effect of DASH diet on pregnancy outcomes in gestational diabetes: a randomized controlled clinical trial. Eur J Clin Nutr. 2014;68(4):490–5.
65. Hernandez TL. Glycemic targets in pregnancies affected by diabetes: historical perspective and future directions. Curr Diab Rep. 2015;15(1):565.
66. McFarland MB, Langer O, Conway DL, Berkus MD. Dietary therapy for gestational diabetes: how long is long enough? Obstet Gynecol. 1999;93(6):978–82.
67. American College of Obstetricians and Gynecologists. ACOG practice bulletin: gestational diabetes, Report number 30; September, 2001. Obstet Gynecol. 2001;98(3):525–38.
68. Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, et al. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest. 1996;97(12):2859–65.
69. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(Supplement 2):S1–8.
70. Major CA, Henry MJ, de Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol. 1998;91(4):600–4.
71. Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial. Diabetes Care. 2009;32(6):996–1000.
72. Louie JC, Markovic TP, Ross GP, Foote D, Brand-Miller JC. Effect of a low glycaemic index diet in gestational diabetes mellitus on post-natal outcomes after 3 months of birth: a pilot follow-up study. Matern Child Nutr. 2015;11(3):409–14.
73. Pastor-Villaescusa B, Rangel-Huerta OD, Aguilera CM, Gil A. A systematic review of the efficacy of bioactive compounds in cardiovascular disease: carbohydrates, active lipids and nitrogen compounds. Ann Nutr Metab. 2015;66(2–3):168–81.
74. Grant SM, Wolever TM, O'Connor DL, Nisenbaum R, Josse RG. Effect of a low glycaemic index diet on blood glucose in women with gestational hyperglycaemia. Diabetes Res Clin Pract. 2011;91(1):15–22.
75. Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. BMJ. 2012;345:e5605.

76. McGowan CA, Walsh JM, Byrne J, Curran S, McAuliffe FM. The influence of a low glycemic index dietary intervention on maternal dietary intake, glycemic index and gestational weight gain during pregnancy: a randomized controlled trial. Nutr J. 2013;12(1):140.
77. Markovic TP, Muirhead R, Overs S, Ross GP, Louie JC, Kizirian N, et al. randomized controlled trial investigating the effects of a low-glycemic index diet on pregnancy outcomes in women at high risk of gestational diabetes mellitus: the GI baby 3 study. Diabetes Care. 2016;39(1):31–8.
78. Kizirian NV, Kong Y, Muirhead R, Brodie S, Garnett SP, Petocz P, et al. Effects of a low-glycemic index diet during pregnancy on offspring growth, body composition, and vascular health: a pilot randomized controlled trial. Am J Clin Nutr. 2016;103(4):1073–82.
79. Louie JC, Buyken AE, Brand-Miller JC, Flood VM. The link between dietary glycemic index and nutrient adequacy. Am J Clin Nutr. 2012;95(3):694–702.
80. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Gestational Diabetes Mellitus. Washington, DC: American College of Obstetricians and Gynecologists; 2013. Report No.: 137.
81. Blumer I, Hadar E, Hadden DR, Jovanovic L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(11):4227–49.
82. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2013;36(11):3821–42.
83. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013 Nov 12.
84. Food and Agriculture Organization of the United Nations. Carbohydrates in human nutrition. Food and Agriculture Organization of the United Nations 1997 (FAO Food and Nutrition Paper-66). Available from: URL: http://www.fao.org/docrep/W8079E/w8079e00.htm#Contents.
85. Nicklas JM, Barbour LA. Optimizing weight for maternal and infant health—tenable, or too late? Expert Rev Endocrinol Metab. 2015;10(2):227–42.

Chapter 34
Polyunsaturated Fatty Acids and Gestational Diabetes

João R. Araújo, Elisa Keating and Fátima Martel

Key Points

- Long-chain polyunsaturated fatty acids play a fundamental role during pregnancy for both the health of the pregnant woman and for the growth and development of the fetus.
- Long-chain polyunsaturated fatty acids regulate placental development and function (angiogenesis, inflammatory status, oxidative stress levels, and hormonal production).
- Maternal-to-fetal placental transfer of long-chain polyunsaturated fatty acids is the major determinant of fetal long-chain polyunsaturated fatty acids bioavailability.
- Gestational diabetes mellitus appears to be associated with a significant decrease in the placental transport of long-chain polyunsaturated fatty acids.
- The decrease in placental transfer of long-chain polyunsaturated fatty acids in gestational diabetes mellitus pregnancies may constitute a possible explanation for the neuro developmental fetal malprogramming associated with this condition.

Keywords Arachidonic acid · Docosahexaenoic acid · Gestational diabetes mellitus · Long-chain acyl-CoA synthetase · Long-chain polyunsaturated fatty acids · Placental transport

Abbreviations

AA	Arachidonic acid
ACSL	Long-chain acyl-CoA synthetase
AMPK	AMP-activated protein kinase
BM	Basal membrane
DHA	Docosahexaenoic acid
EL	Endothelial lipase
EPA	Eicosapentaenoic acid

J.R. Araújo
Unité de Pathogénie Microbienne Moléculaire Institut Pasteur,
28, rue du Dr Roux, Paris, France
e-mail: joao.diniz-de-araujo@pasteur.fr

E. Keating
Department of Biochemistry, Faculty of Medicine CINTESIS, Center for Research
in Health Technologies and Information Systems, University of Porto, Porto, Portugal
e-mail: keating@med.up.pt

F. Martel (✉)
Department of Biochemistry, Faculty of Medicine, Institute for Research and Innovation
in Health Sciences, University of Porto, Porto, Portugal
e-mail: fmartel@med.up.pt

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_34

FABP	Fatty acid binding proteins
FAT/CD36	Fatty acid translocase
FATP	Fatty acid transport proteins
FGR	Fetal growth restriction
GDM	Gestational diabetes mellitus
HOMA	Homoeostasis model of assessment
HSL	Hormone sensitive lipase
LA	Linoleic acid
LC-PUFA	Long-chain polyunsaturated fatty acid
LC-PUFAs	Long-chain polyunsaturated fatty acids
LNA	α-linolenic acid
LPL	Lipoprotein lipase
LXRα	Liver X receptor α
MVM	Microvillous membrane
pFABPpm	Placental plasma membrane fatty acid binding protein
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
RXRα	Retinoid X receptor
SREBP1c	Sterol regulatory element-binding transcription factor 1c
STB	Syncytiotrophoblast
TNFα	Tumor necrosis factor alpha
VLDL	Very low density lipoprotein

Importance of LC-PUFAS for Pregnancy

From a physiological point of view, long-chain polyunsaturated fatty acids (LC-PUFAs) of the n-3 and n-6 series, such as arachidonic (AA; 20:4n-6), docosahexaenoic (DHA; 22:6n-3), and eicosapentaenoic acids (EPA; 20:5n-3) (Fig. 34.1), are the most important fatty acids for fetal growth and development [1, 2]. Apart from serving as energy substrates, LC-PUFAs are essential components of cellular membranes, maintaining their appropriate structure, fluidity, and permeability, being thus fundamental for impulse propagation and synaptic transmission [3]. Also, they can act as regulators of gene expression via transcription factors (e.g., the nuclear receptors PPARα, beta, and gamma) [4] and DNA methylation (Fig. 34.2) [5].

LC-PUFAs are also precursors for the synthesis of eicosanoids such as prostaglandins, thromboxanes, and leukotrienes, which are critically important for the development of fetal nervous, visual, immune and vascular systems, [6, 7] and also for labor [8]. DHA, in particular, has been found to be essential for the development of the fetal neurovisual system, being highly concentrated in the brain and retina of the newborn [6, 7]. Moreover, through the conversion of phosphatidylethanolamine-DHA to phosphatidylcholine-DHA, DHA levels regulate methyl group availability (Fig. 34.2) [5].

The importance of LC-PUFAS for fetal development is well demonstrated by the fact that its depletion in fetal tissues is associated with cognitive, behavioral, and visual abnormalities later in life [1]. Also, insufficient maternal consumption of n-3 and n-6 fatty acids during pregnancy is often correlated with preterm birth or fetal growth restriction (FGR) [9, 10]. Importantly, animal studies demonstrated that DHA deficiency during gestation and soon after birth cannot be fully corrected later in life [11]. In accordance with these evidences, maternal LC-PUFAs supplementation during pregnancy was found to improve neurodevelopmental (cognitive and visual) functions in infants [12, 13] while reducing the risk of preterm delivery [14] and low birth weight [13–15].

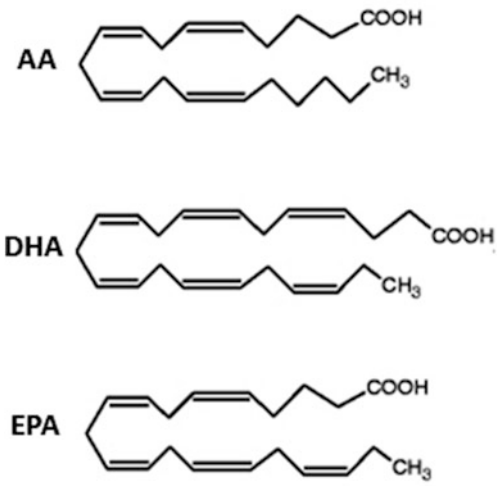


Fig. 34.1 Structure of arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid. *Legend AA* arachidonic acid; *DHA* docosahexaenoic acid; *EPA* eicosapentaenoic acid

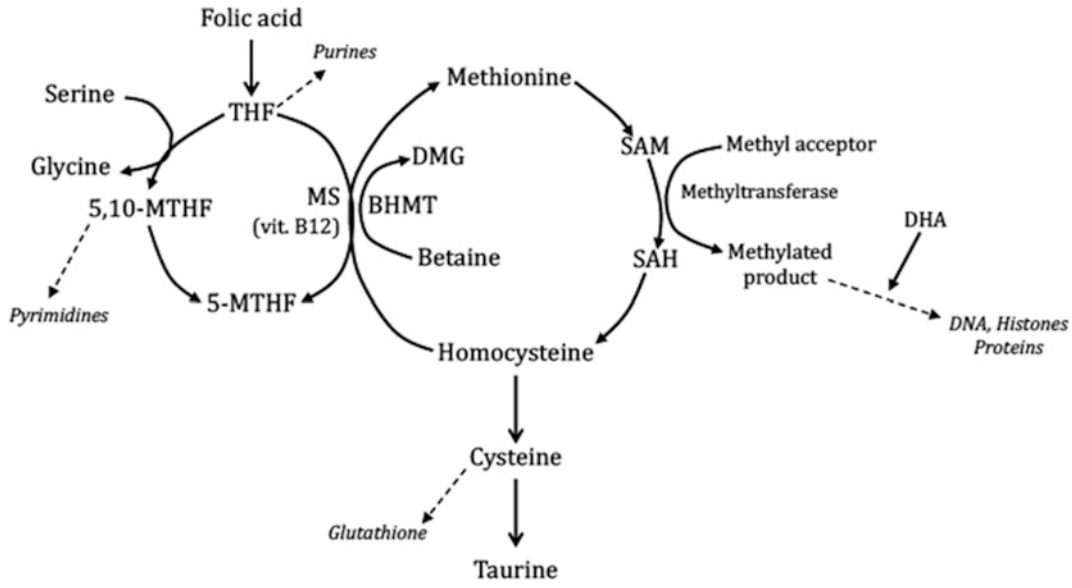


Fig. 34.2 Interaction of folic acid, methionine, and docosahexaenoic acid in one carbon cycle. *Legend* 5,10-*MTHF* N^5, N^{10}-methylenetetrahydrofolate; *5-MTHF* N^5-methyltetrahydrofolate; *BHMT* betaine–homocysteine methyltransferase; *DHA* docosahexaenoic acid; *DMG* dimethylglycine; *MS* methionine synthase; *SAH* S-adenosylhomocysteine; *SAM* S-adenosylmethionine; *THF* tetrahydrofolate; vit B_{12}, vitamin B_{12}

Moreover, supplementation of maternal diet with n-3 LC-PUFAs during pregnancy reduced the risk of macrosomia and later-in-life obesity [16]. Based on this, the European Food Safety Authority (EFSA) recommends that maternal intake of LC-PUFAs should be increased during pregnancy and lactation [17].

However, it should be noted that not all studies found a consistent association between maternal intake of LC-PUFAs and good pregnancy outcomes [e.g., 18–20]. These differences may be related to

the nature of LC-PUFA ingested, dose, type of supplement, and on the outcome evaluation. Also, lack of positive outcome may be due to the inhibitory effect of a given LC-PUFA on the enzymatic synthesis (involving delta 6- and delta 5-desaturases) of other LC-PUFAs [2, 21]. So, the efficacy of LC-PUFAs supplements (and in particular n-3 LC-PUFAs) to reduce the risk of preterm birth and low birth weight needs further work.

A few studies have investigated the relationship between LC-PUFA supplementation during pregnancy and diabetes. Maternal dietary supplementation with n-3 PUFA during pregnancy was found to have a positive action on insulin function, with an improvement of glucose tolerance [22, 23]. In another study, supplementation with DHA ameliorated red cell membrane anomaly in pregnant women with T2D and in neonates [24]. Finally, GDM women who received n-3 LC-PUFA supplementation showed a significant decrease in serum insulin levels and in HOMA index (homoeostasis model of assessment–IR) [25] and better newborn outcome [26], compared with placebo groups. It has been hypothesized that n-3 PUFA supplementation might affect insulin metabolism and lipid profiles by activating AMPK [27].

Role of LC-PUFAs in the Placenta

The placenta constitutes the main interface between the maternal and fetal circulations and performs multiple functions required for fetal growth and development, such as exchange of nutrients and metabolites and the production and metabolism of several hormones and growth factors. Recent data indicate that LC-PUFAs play an important role in placental development and function.

Placentation Normal placental development relies on a balanced growth, proliferation, differentiation, invasion, and programmed cell death of trophoblasts. Impaired placental development due to reduced trophoblast invasion and angiogenesis is associated with preeclampsia and fetal growth restriction (FGR), and GDM is also associated with changes in trophoblast proliferation and apoptosis [28–30]. Interestingly, LC-PUFAs possess angiogenic activities [31, 32]; of these, DHA appears to possess the greatest stimulatory effect on angiogenesis and tube formation [31, 32]. The angiogenic activity of LC-PUFAs is apparently mediated by prostaglandins [33] and PPARγ [34] and involves increased expression of FABP1-4 [31, 32]. Inactivation of PPARγ leads to irreversible arrest of trophoblast differentiation, early embryonic lethality, and severe developmental placental damage [35, 36]. So, LC-PUFAs, via PPARγ, appear to play a very important role during implantation and placentation.

Inflammation Pregnancy-related inflammation is considered beneficial for a successful pregnancy, but excessive placental inflammation is associated with unfavorable pregnancy outcomes such as preterm birth, preeclampsia, FGR [37] and GDM [38]. LC-PUFAs are the precursors of eicosanoids, inflammatory mediators that include prostaglandins, leukotrienes, and thromboxanes. AA-derived (n-6) eicosanoids are mainly proinflammatory, acting to enhance local blood flow and to increase the production of proinflammatory citokines and reactive oxygen species. In contrast, eicosanoids derived from DHA and EPA (n-3) generally have anti-inflammatory properties. LC-PUFAs thus can modulate the balance between proinflammatory and anti-inflammatory effects at the placental level [39]. Animal studies have demonstrated that n-3 fatty acids supplementation can normalize increased placental inflammatory cytokine levels resulting from micronutrient imbalance [40] and is able to increase the placental levels of the proresolving mediators resolvin and protectin while decreasing the systemic levels of proinflammatory cytokine TNFα [41]. Importantly, n-3 fatty acid supplementation was able to decrease serum levels of an inflammatory marker (high sensitivity C-reactive protein), in GDM women [25].

Oxidative stress Although pregnancy is a state of increased oxidative stress due to the high metabolic activity of the placenta, pregnancy-related diseases such as GDM are associated with abnormal increases in oxidative stress levels [42]. N-3 PUFAs could theoretically limit oxidative stress by enhancing reactive oxygen species (ROS) scavenging capacity and/or by limiting ROS production [43–45], but the results obtained with supplementation of maternal diet with n-3 PUFAs have not been consistent: either an antioxidant effect [46, 47], no effect [48], or a proxidant effect [49] were described. So, although a recent review suggests that maternal dietary n-3 fatty acid supplementation may limit placental oxidative stress associated with several pregnancy disorders [50], the role of LC-PUFAs in placental oxidative stress is still controversial.

Influence on adipokines The placenta can produce adipokines such as leptin and adiponectin [51]. Interestingly enough, an increase in the expression of placental leptin and its receptor genes has been found in pregnancies associated with GDM [52]. Supplementation with n-3 PUFAs is associated with reduced levels of circulating leptin [53], and although LC-PUFAs could theoretically regulate the concentration of adiponectin through PPARγ, only a modest increase in adiponectin concentration has been observed after maternal diet supplementation with n-3 PUFAs [54]. So, more studies are necessary to confirm this relationship.

Sources of LC-PUFAs to the Fetus

LC-PUFAs (ARA, EPA and DHA) can be obtained by ingesting foods of animal origin, but they can also be obtained in the body after metabolism of linoleic (18:2n-6; LA) and linolenic (18:3n-3; LNA) acids, two nutritionally essential fatty acids readily available from dietary sources such as vegetable oils (Fig. 34.3). LA and LNA are the precursors of the LC-PUFAs of the n-6 and n-3 pathways, respectively, which are synthesized by elongation and desaturation (Fig. 34.3). So, the sources of LC-PUFAs to sustain fetal growth can be both maternal diet and fat stores and fetal synthesis. However, the fetal conversion of essential fatty acids to LC-PUFAs is very limited [55] and the placenta (the organ involved in the maternal-to-fetal transfer of nutrients) has no capacity to convert essential fatty acids into other LC-PUFAs, due to the lack or very low activity of desaturases [56]. So, during intrauterine life, LC-PUFAs may be also considered as essential for the fetus. Indeed, the amount of n-3 fatty acids in the fetus is correlated with the amount ingested by the mother [57]. In this regard, it is important to note that GDM associates with an altered maternal lipid profile and affects the quantity and/or quality of lipids transferred to the fetus [58]. In GDM, a positive correlation between maternal TAG and non-esterified fatty acid levels and fetal growth and fat mass has been found, even in diabetic mothers with appropriate glycemic control [58].

During the intrauterine period, the accumulation of lipids and of specific fatty acids is relatively small but increases logarithmically with gestational age, and reaches its maximal rate of accretion just before term [3]. So, during the earliest stages of intrauterine life and until the 25th week of gestation, the net rate of LC-PUFA utilization by the fetus does not make a significant additional demand on the maternal diet. However, the requirement increases greatly thereafter to reach it maximum close to the term [3]. Of importance, a substantial proportion of mothers during the late stages of gestation do not ingest enough preformed LC-PUFAs to meet maternal and fetal needs [59].

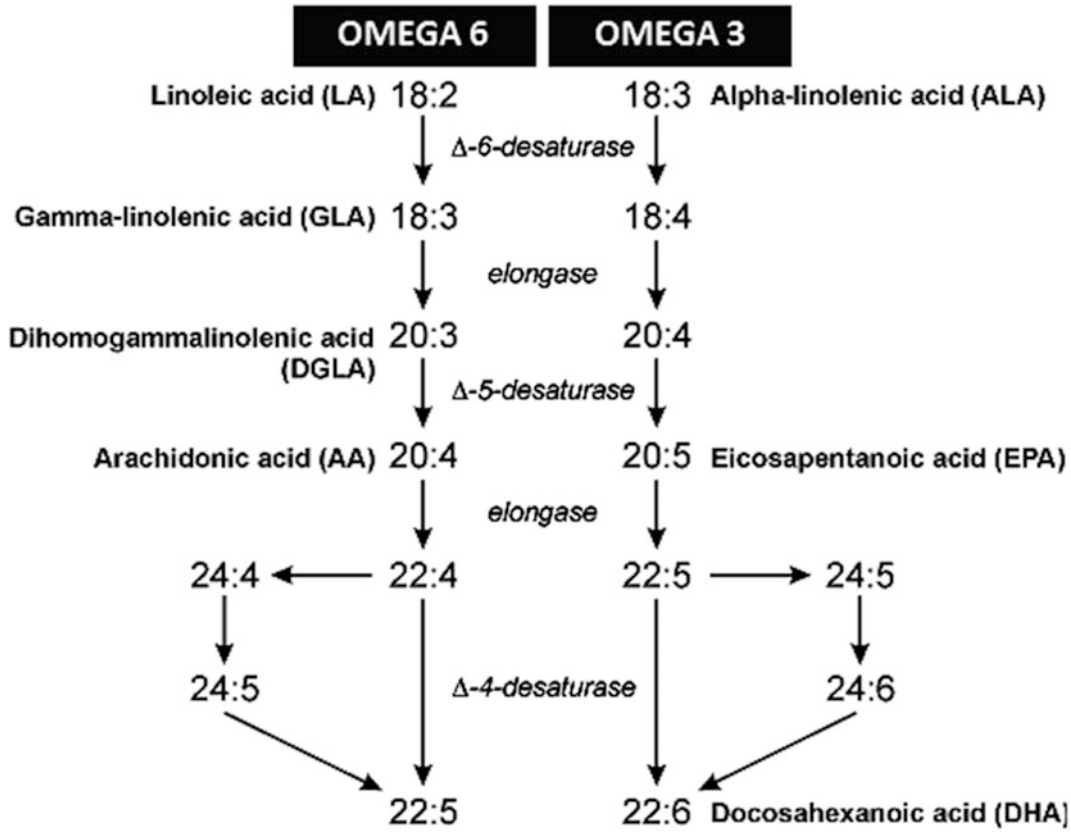


Fig. 34.3 Schematic n-6 and n-3 pathways for the synthesis of arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid from the dietary essential fatty acids, linoleic acid, and α-linolenic acid. *Legend AA* arachidonic acid; *EPA* eicosapentaenoic acid; *DHA* docosahexaenoic acid; *LA* linoleic acid; *ALA* linolenic acid

Mechanisms Involved in the Placental Transport of LC-PUFAs

To assure an optimal growth and development of the fetus, an adequate supply of LC-PUFAs from maternal to the fetal circulation is mandatory [3, 7, 60]. Most LC-PUFAs are present at higher concentrations in fetal than in maternal circulation [61]—a phenomenon termed biomagnification [62]. Consequently, toward the end of the pregnancy, their levels are several times higher in fetal adipose tissue than in the maternal adipose tissue [63]. This phenomenon is thought to be the result of a selective and more efficient placental transport of LC-PUFAs (in particular AA and DHA) [64, 65], over non-essential shorter fatty acids, in favor of the fetus [3, 7].

The syntitiotrophoblast (STB) epithelium is the most important placental tissue actively involved in the maternal-to-fetal transport of nutrients, including lipids [63, 66, 67]. Although LC-PUFAs can be transported in the plasma in a nonsterified form (bound to albumin), LC-PUFAs transported across the human STB are mainly derived from triglyceride-rich lipoproteins (VLDL), from which they are released by the action of placental lipases [61]. So, placental lipases such as lipoprotein lipase (LPL), endothelial lipase (EL) and hormone sensitive lipase (HSL) are involved in the transfer of lipids from mother to fetus (Fig. 34.4). Previous studies of expression of these lipases in placenta in women with diabetes in pregnancy have reported divergent results. An increase in lipase expression was observed in maternal type I diabetes, whereas no significant changes were found in GDM [68–70], although

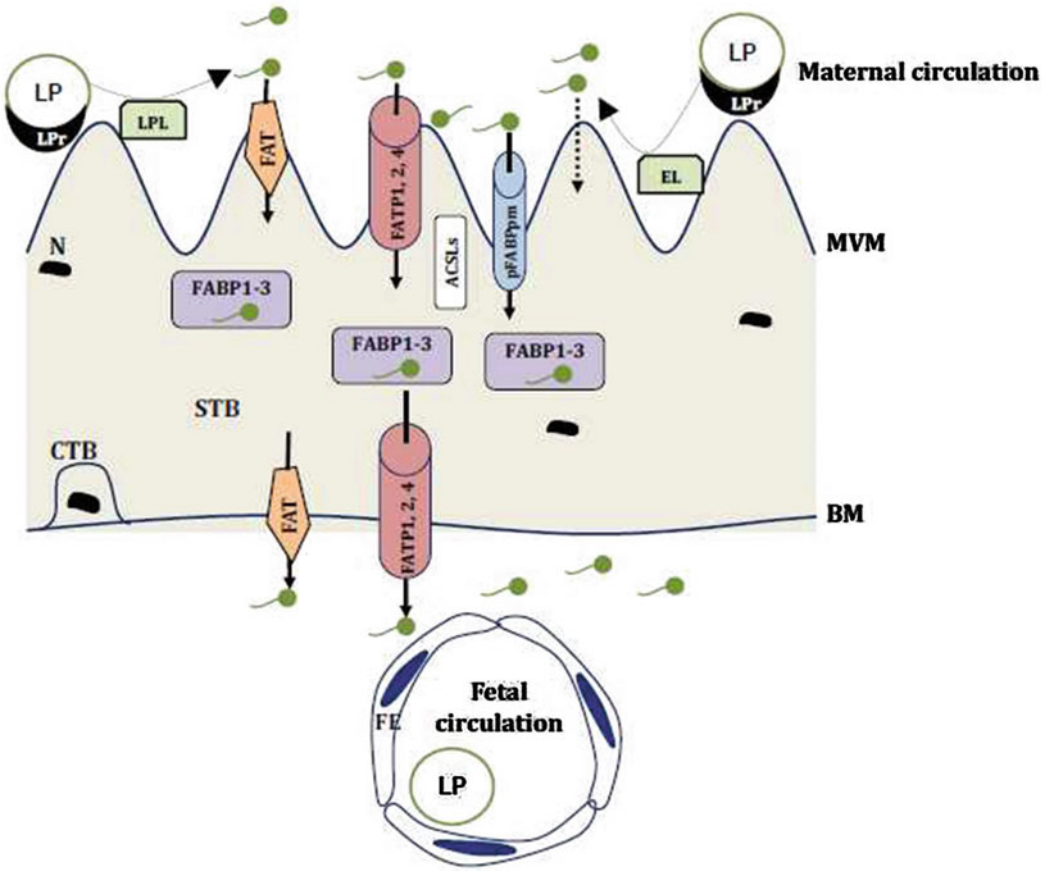


Fig. 34.4 Long-chain polyunsaturated fatty acids (LC-PUFAs) transport at the human syncytiotrophoblast. *Legend* LC-PUFA; *ACSL* long-chain acyl-CoA synthetases; *BM* basal membrane; *CTB* cytotrophoblast; *FATP* fatty acid transport proteins; FAT/CD36: fatty acid translocase; *EL* endothelial lipase; *FE* fetal endothelium; *LP* lipoprotein; *LPL* lipoprotein lipase; *LPr* lipoprotein receptor; *MVM* microvillous membrane; *N* nucleus; *pFABPpm* placental plasma membrane fatty acid binding protein; *STB* syncytiotrophoblast

increased EL mRNA was found in placenta from obese women with GDM compared with lean GDM women or normoglycemic pregnant women [71].

Although LC-PUFAs can be taken up by the STB via passive diffusion, membrane-associated fatty acid transport proteins are also implicated in this transport process. Namely, placental plasma membrane fatty acid binding protein (pFABPpm), fatty acid transport proteins (FATP), and fatty acid translocase (FAT/CD36) [3, 7]. Additionally, intracellular fatty acid binding proteins (FABP), in particular FABP 1, 3, and 4, are responsible for directing fatty acids to their specific intracellular locations [6, 7] (Fig. 34.4). The precise mechanisms by which these transport proteins facilitate transmembrane passage of LC-PUFAs are still a matter of speculation.

pFABPpm is a 40 kDa unidirectional placenta-specific transporter with preferential affinity for LC-PUFAs such as DHA and AA, and is found exclusively on the MVM of term STB (Table 34.1; Fig. 34.4) [6, 7].

The 63–70 kDa FATP family (FATP1–6) transports fatty acids in an ATP-dependent manner with no preference for any particular LC-PUFA [7, 72]. FATP1, 2, and 4 are expressed in the MVM and BM of the human STB [6] (Table 34.1; Fig. 34.4). A still ongoing debate about FATP is whether

Table 34.1 Long-chain polyunsaturated fatty acids transporters in the human term placenta

Transport system	Isoform	STB localization	Substrates	References
pFABPpm	?	MVM	LC-PUFAs	[6, 7]
FATP	FATP1,2,6	MVM, BM	Long-chain fatty acids	[6, 7]
FAT/CD36	–	MVM, BM	Long-chain fatty acids	[3, 6]
ACSL	ACSL1,3,4,5,6	Cytosol	LC-PUFAs	[6]
FABP	FABP1,3,4	Cytosol	LC-PUFAs	[3, 6]

ACSL long-chain acyl-CoA synthetase; *BM* basal membrane; *FABP* fatty acid binding proteins; *FAT/CD36* fatty acid translocase; *FATP* fatty acid transport proteins; *LC-PUFAs* long-chain polyunsaturated fatty acids; *MVM* microvillous membrane; *pFABPpm* placental plasma membrane fatty acid binding protein; *STB* syncytiotrophoblast

they act solely as transmembrane transport proteins or if they also harbor long-chain acyl-CoA synthetase (ACSL) activity [7, 73]. ACSL are a group of cytosolic enzymes that prevent the efflux of intracellular fatty acids by converting them into acyl-CoA derivatives for further esterification or β-oxidation [74, 75]. These enzymes, in particular ACSL1, 3, 4, 5, and 6, have been proven to be involved in LC-PUFAs uptake by trophoblasts [3, 7, 60].

FAT/CD36 is a 88 kDa glycoprotein receptor that allows bidirectional and non-selective transport of fatty acids, being expressed in both membranes of the STB (Table 34.1; Fig. 34.4) [3]. Unlike pFABPpm and FATP, FAT is a multifunctional protein that interacts with a number of ligands such as free fatty acids, collagen, thrombospondin, and oxidized LDL [76]. At present, it is still arguable if FAT/CD36 is really important for AA and DHA placental transport [6].

Uptake of fatty acids has been studied in in vitro cellular models of villous (Bewo cells) and extravillous (HTR8/SVneo) trophoblasts. Interestingly enough, uptake of LC-PUFAs was strongly inhibited by triacsin C, an inhibitor of CoA formation catalyzed by acyl-CoA synthetase, in both cell lines [29, 31, 77]. This strongly indicates that the CoA formation step is involved in the uptake of these fatty acids in both villous and extravillous human trophoblasts.

The presence of several distinct cytoplasmatic fatty acid binding proteins (heart type (H-FABP) and liver-type (L-FATP)) has been reported in human placental trophoblasts. The significance of the presence of several cytoplasmatic FABPs in trophoblasts is not known but they participate in intracellular transport and metabolism of fatty acids, especially in the conversion of the n-3 and n-6 series to their respective derivatives. So, interaction of fatty acids with these proteins may be essential for effective fatty acid transport and metabolism [7].

The manner in which placental LC-PUFAs are released into the fetal circulation is not completely understood. They may be either released into fetal circulation in the form of nonsterified fatty acids, then combining with albumin or alpha-fetoprotein [78] or they may be released in their esterified form, associated with specific lipoproteins [79, 80].

Placental fatty acid metabolism may also play a critical role in fetal availability of LC-PUFAs, as a selective metabolism will impact their placental transfer process. LC-PUFAs can be oxidized in the placenta (fatty acids appear to be an important placental metabolic fuel) [81], incorporated into phospholipids and triacylglycerols or converted into signaling molecules (e.g., prostaglandins) [82] by enzymes such as cyclooxigenases, lipoxygenases, and cytochrome P450 subfamily 4A [81].

Alteration of Placental Transport of LC-PUFAs in GDM

Alterations in placental LC-PUFAs transport were described to occur in pregnancies complicated by GDM (Table 34.2). An upregulation in the expression levels of FABP1, 3 and 4 [68, 83] and of ACSL2, 3, and 4 [83] have been described to occur in GDM placentas [68, 71]. However, lower

Table 34.2 Effect of gestational diabetes mellitus and its associated conditions on the placental uptake of long-chain polyunsaturated fatty acids in human placenta

	LC-PUFAs uptake	References
GDM	↓	[29]
Glucose	=	[29]
Insulin	= or •	[29, 87]
Leptin	=	[29, 87]
Proinflammatory mediators	= or •	[29, 88]

• increase; ↓ decrease; = no change; LC-PUFAs, long-chain polyunsaturated fatty acids; GDM, gestational diabetes mellitus

concentrations of AA and DHA were observed in placentas [80] and cord blood samples [80, 84, 85] from GDM compared with normal pregnancies, suggesting that placental transport of LC-PUFAs may be impaired in GDM [58]. In agreement with this suggestion, uptake of DHA and AA were found to be markedly reduced ($\geq 50\%$) in primary cultured trophoblast derived from GDM pregnancies, when compared with those derived from normal pregnancies [29]. Interestingly enough, the decrease in LC-PUFAS uptake in GDM-derived trophoblasts was associated with a quantitatively similar reduction in ACSL1 mRNA levels, indicating that the reduction in its expression underlies the decrease in AA and DHA uptake [29]. Very interestingly, a decreased expression of genes involved in fatty acid cellular uptake and intracellular transport (e.g., LPL, FATP2, FATP6, FABPpm, ACSL1), and of transcription factors involved in lipid metabolism regulation (e.g., liver X receptor (LXRα), PPARα, PPARδ, PPARγ, RXRα, SREBP1c) has been observed in adipose tissue obtained from obese pregnant women and women with GDM [86]. This suggests a common mechanism mediating a reduction in the cellular uptake of LC-PUFAs both in the mother and fetus during GDM.

The effect of GDM-associated conditions on the placental transport of LC-PUFAs has been investigated in a few studies, and so knowledge on this subject remains very limited (Table 34.2). In human cultured trophoblasts, high levels of glucose [29] and leptin were shown not to affect AA and DHA uptake [29, 87]. In contrast, uptake of AA and DHA was found to be increased after: (a) short- [29] but not long-term [88] exposure to high levels of TNF-α, (b) long-term exposure to high levels of IL-6 (by a FATP-independent mechanism) [88], and (c) short- [29] but not long-term exposure [87] to high levels of insulin. The completely contrasting effects of GDM conditions upon LC-PUFA uptake in human trophoblasts (increase or no alteration) and the transport of these fatty acids in GDM-derived trophoblasts (decrease) imply that the regulatory effect of GDM upon placental transport of LC-PUFAs cannot be attributed to a single GDM condition but rather to a complex interaction among multiple conditions.

Conclusions

LC-PUFAs play a key role in fetal development, being particularly important for the structure and function of the nervous and visual system. They are important for fetal growth, their oxidation plays an essential role as a source of energy for the fetoplacental unit, and they are precursors of bioactive compounds. They also regulate placental development and function and are involved in the demanding pro-inflammatory/anti-inflammatory balance characteristic of pregnancy.

GDM and its associated conditions may compromise LC-PUFA placental transport and thus delivery to the feto-placental unit. This molecular mechanism may at least in part underlie the deleterious effects of GDM on placental development, function and inflammatory and redox homeostasis. Moreover, and importantly, given the crucial role of LC-PUFAs in the development of the

visual and cognitive function in the fetus, the decrease in placental transfer of LC-PUFAs in GDM pregnancies may constitute a possible explanation for the neurodevelopmental fetal malprogramming associated with GDM.

References

1. Innis SM. Essential Fatty acids transfer and foetal development. Placenta. 2005;26:70–5.
2. Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations World Association of Perinatal Medicine Dietary Guidelines Working Group. J Perinatal Med. 2008;36:5–14.
3. Haggarty P. Fatty acid supply to the human fetus. Annu Rev Nutr. 2010;30:237–55.
4. Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. Prog Lipid Res. 2008;47:147–55.
5. Kulkarni A, Dangat K, Kale A, et al. Effects of altered maternal folic acid, vitamin B12 and docosahexaenoic acid on placental global DNA methylation patterns in Wistar rats. PLoS ONE. 2011;6:e17706.
6. Cunningham P, McDermott L. Long chain PUFA transport in human term placenta. J Nutr. 2009;139:636–9.
7. Duttaroy AK. Transport of fatty acids across the human placenta: a review. Prog Lipid Res. 2009;48:52–61.
8. Allen KG, Harris MA. The role of n-3 fatty acids in gestation and parturition. Exp Biol Med. (Maywood). 2001;226:498–506.
9. Cetin I, Giovannini N, Alvino G, et al. Foetal-maternal fatty acid relationships in normal pregnancies and in pregnancies associated with intrauterine growth restriction (IUGR). J Soc Gynecol Invest. 2001;8:254.
10. Cetin I, Giovannini N, Alvino G, et al. Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal-maternal relationships. Pediatr Res. 2002;52:750–5.
11. Krabbendam L, Bakker E, Hornstra G, et al. Relationship between DHA status at birth and child problem behaviour at 7 years of age. Prostaglandins Leukot Essent Fatty Acids. 2007;76:29–34.
12. Ryan AS, Astwood JD, Gautier S, et al. Effects of long-chain polyunsaturated fatty acid supplementation on neurodevelopment in childhood: a review of human studies. Prostaglandins Leukot Essent Fatty Acids. 2010;82:305–14.
13. Larque E, Gil-Sanchez A, Prieto-Sanchez MT, et al. Omega 3 fatty acids, gestation and pregnancy outcomes. Br J Nutr. 2012;107:S77–84.
14. Greenberg JA, Bell SJ, Ausdal WV. Omega-3 Fatty Acid supplementation during pregnancy. Rev Obstet Gynecol. 2008;1:162–9.
15. Carlson SE, Colombo J, Gajewski BJ, et al. DHA supplementation and pregnancy outcomes. Am J Clin Nutr. 2013;97:808–15.
16. Yessoufou A, Nekoua MP, Gbankoto A, et al. Beneficial effects of omega-3 polyunsaturated Fatty acids in gestational diabetes: consequences in macrosomia and adulthood obesity. J Diabetes Res. 2015;2015:731434.
17. EFSA. Outcome of the Public consultation on the Draft Opinion of the Scientific Panel on Dietetic products, Nutrition, and Allergies (NDA) on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. EFSA J. 2010;8:1507.
18. Rogers I, Emmett P, Ness A, et al. Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. J Epidemiol Community Health. 2004;58:486–92.
19. Ramakrishnan U, Stein AD, Parra-Cabrera S, et al. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: Randomized, double-blind, placebo-controlled trial in Mexico. Food Nutr Bull. 2010;31(2 Suppl):S108–16.
20. Brantsaeter AL, Birgisdottir BE, Meltzer HM, et al. Maternal seafood consumption and infant birth weight, length and head circumference in the Norwegian Mother and Child Cohort Study. Br J Nutr. 2012;107:436–44.
21. Raz A, Belsky NK, Przedecki F, et al. Fish oil inhibits Δ6 desaturase activity in vivo: utility in a dietary paradigm to obtain mice depleted of arachidonic acid. J Nutr Biochem. 1997;8:558–65.
22. Lu J, Borthwick F, Hassanali Z, et al. Chronic dietary n-3 PUFA intervention improves dyslipidaemia and subsequent cardiovascular complications in the JCR:LA-cp rat model of the metabolic syndrome. Br J Nutr. 2011;105:1572–82.
23. Mohammadi E, Rafraf M, Farzadi L, et al. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. Asia Pac J Clin Nutr. 2012;21:511–8.
24. Min Y, Djahanbakhch O, Hutchinson J, et al. Effect of docosahexaenoic acid-enriched fish oil supplementation in pregnant women with type 2 diabetes on membrane fatty acids and fetal body composition-double-blinded randomized placebo-controlled trial. Diabet Med. 2014;31:1331–40.

25. Samimi M, Jamilian M, Asemi Z, et al. Effects of omega-3 fatty acid supplementation on insulin metabolism and lipid profiles in gestational diabetes: randomized, double-blind, placebo-controlled trial. Clin Nutr. 2015;34: 388–93.
26. Jamilian M, Samimi M, Kolahdooz F, et al. Omega-3 fatty acid supplementation affects pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebocontrolled trial. J Matern Fetal Neonatal Med. 2016;29:669–75.
27. Higuchi T, Shirai N, Saito M, et al. Levels of plasma insulin, leptin and adiponectin, and activities of key enzymes in carbohydrate metabolism in skeletal muscle and liver in fasted ICR mice fed dietary n-3 polyunsaturated fatty acids. J Nutr Biochem. 2008;19:577–86.
28. Sgarbosa F, Barbisan LF, Brasil MA, et al. Changes in apoptosis and Bcl-2 expression in human hyperglycemic, term placental trophoblast. Diabetes Res Clin Pract. 2006;73:143–9.
29. Araújo JR, Correia-Branco A, Ramalho C, et al. Gestational diabetes mellitus decreases placental uptake of long chain polyunsaturated fatty acids: involvement of long-chain acyl-CoA synthetase. J Nutr Biochem. 2013;24:1741–50.
30. Belkacemi L, Kjos S, Nelson DM, et al. Reduced apoptosis in term placentas from gestational diabetic pregnancies. J Dev Orig Hlth Dis. 2013;4:256–65.
31. Basak S, Duttaroy AK. Effects of fatty acids on angiogenic activity in the placental extravillious trophoblast cells. Prostaglandins Leukot Essent Fatty Acids. 2013;88:155–62.
32. Johnsen GM, Basak S, Weedon-Fekjaer MS, et al. Docosahexaenoic acid stimulates tube formation in first trimester trophoblast cells, HTR8/SVneo. Placenta. 2011;32:626–32.
33. Finetti F, Solito R, Morbidelli L, et al. Prostaglandin E2 regulates angiogenesis via activation of fibroblast growth factor receptor-1. J Biol Chem. 2008;283:2139–46.
34. Nadra K, Quignodon L, Sardella C, et al. PPARgamma in placental angiogenesis. Endocrinology. 2010;151: 4969–81.
35. Barak Y, Liao D, He W, et al. Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. Proc Natl Acad Sci USA. 2002;99:303–8.
36. Yessoufou A, Hichami A, Besnard P, et al. Peroxisome proliferator-activated receptor alpha deficiency increases the risk of maternal abortion and neonatal mortality in murine pregnancy with or without diabetes mellitus: modulation of T cell differentiation. Endocrinology. 2006;147:4410–8.
37. Cotechini T, Graham CH. Aberrant maternal inflammation as a cause of pregnancy complications: a potential therapeutic target? Placenta. 2015;36:960–6.
38. Lekva T, Norwitz ER, Aukrust P, et al. Impact of Systemic Inflammation on the Progression of Gestational Diabetes Mellitus. Curr Diab Rep. 2016;16:26.
39. Yamashita A, Kawana K, Tomio K, et al. Increased tissue levels of omega-3 polyunsaturated fatty acids prevents pathological preterm birth. Sci Rep. 2013;3:3113.
40. Meher AP, Joshi AA, Joshi SR. Maternal micronutrients, omega-3 fatty acids, and placental PPARγ expression. Appl Physiol Nutr Metab. 2014;39:793–800.
41. Jones ML, Mark PJ, Keelan JA, et al. Maternal dietary omega-3 fatty acid intake increases resolvin and protectin levels in the rat placenta. J Lipid Res. 2013;54:2247–54.
42. Pereira AC, Martel F. Oxidative stress in pregnancy and fertility pathologies. Cell Biol Toxicol. 2014;30:301–12.
43. Wang H-H, Hung T-M, Wei J, et al. Fish oil increases antioxidant enzyme activities in macrophages and reduces atherosclerotic lesions in apoE-knockout mice. Cardiovasc Res. 2004;61:169–76.
44. Gorjão R, Azevedo-Martins AK, Rodrigues HG, et al. Comparative effects of DHA and EPA on cell function. Pharmacol Ther. 2009;122:56–64.
45. Lluís L, Taltavull N, Muñoz-Cortés M, et al. Protective effect of the omega-3 polyunsaturated fatty acids: Eicosapentaenoic acid/Docosahexaenoic acid 1:1 ratio on cardiovascular disease risk markers in rats. Lipids Health Dis. 2013;12:1–8.
46. Jones ML, Mark PJ, Lewis JL, et al. Antioxidant defenses in the rat placenta in late gestation: Increased labyrinthine expression of superoxide dismutases, glutathione peroxidase 3, and uncoupling protein 2. Biol Reprod. 2010;83:254–60.
47. Jones ML, Mark PJ, Mori TA, et al. Maternal dietary omega-3 fatty acid supplementation reduces placental oxidative stress and increases fetal and placental growth in the rat. Biol Reprod. 2013;88:37.
48. Stark MJ, Clifton VL, Hodyl NA. Differential effects of docosahexaenoic acid on preterm and term placental pro-oxidant/antioxidant balance. Reproduction. 2013;146:243–51.
49. Boulis TS, Rochelson B, Novick O, et al. Omega-3 polyunsaturated fatty acids enhance cytokine production and oxidative stress in a mouse model of preterm labor. J Perinat Med. 2014;42:693–8.
50. Jones ML, Mark PJ, Waddell BJ. Maternal dietary omega-3 fatty acids and placental function. Reproduction. 2014;147:R143–52.
51. Ahlsson F, Diderholm B, Ewald U, et al. Adipokines and their relation to maternal energy substrate production, insulin resistance and fetal size. Eur J Obstet Gynecol Reprod Biol. 2013;168:26–9.

52. Pérez-Pérez A, Maymó JL, Gambino YP, et al. Activated translation signaling in placenta from pregnant women with gestational diabetes mellitus: possible role of leptin. Horm Metab Res. 2013;45:436–42.
53. Hariri M, Ghiasvand R, Shiranian A, et al. Does omega-3 fatty acids supplementation affect circulating leptin levels? A systematic review and meta-analysis on randomized controlled clinical trials. Clin Endocrinol (Oxford). 2014;80:221–8.
54. von Frankenberg AD, Silva FM, de Almeida JC, et al. Effect of dietary lipids on circulating adiponectin: A systematic review with meta-analysis of randomised controlled trials. Br J Nutr. 2014;112:1235–50.
55. Duttaroy AK. Transport mechanisms for long-chain polyunsaturated fatty acids in the human placenta. Am J Clin Nutr. 2000;71:315S–22S.
56. Cetin I, Alvino G. Intrauterine growth restriction: implications for placental metabolism and transport. Placenta. 2009;30:77–82.
57. Helland IB, Smith L, Blomen B, et al. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. Pediatrics. 2008;122:e472–9.
58. Herrera E, Ortega-Senovilla H. Disturbances in lipid metabolism in diabetic pregnancy—are these the cause of the problem? Best Pract Res Clin Endocrinol Metab. 2010;24:515–25.
59. Welch AA, Shakya-Shrestha S, Lentjes MA, et al. Dietary intake and status of n-3 polyunsaturated fatty acids in a population of fish-eating and non-fish-eating meat-eaters, vegetarians, and vegans and the product–precursor ratio (corrected) of alpha-linolenic acid to long-chain n-3 polyunsaturated fatty acids: Results from the EPIC-Norfolk cohort. Am J Clin Nutr. 2010;92:1040–1.
60. Johnsen GM, Weedon-Fekjaer MS, Tobin KA, et al. Long-chain polyunsaturated fatty acids stimulate cellular fatty acid uptake in human placental choriocarcinoma (BeWo) cells. Placenta. 2009;30:1037–44.
61. Hanebutt FL, Demmelmair H, Schiessl B, et al. Long-chain polyunsaturated fatty acid (LC-PUFA) transfer across the placenta. Clin Nutr. 2008;27:685–93.
62. Larque E, Demmelmair H, Gil-Sanchez A, et al. Placental transfer of fatty acids and fetal implications. Am J Clin Nutr. 2011;94:1908S–13S.
63. Jansson T, Myatt L, Powell TL. The role of trophoblast nutrient and ion transporters in the development of pregnancy complications and adult disease. Curr Vasc Pharmacol. 2009;7:521–33.
64. Al MD, van Houwelingen AC, Kester AD, et al. Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. Br J Nutr. 1995;74:55–68.
65. Berghaus TM, Demmelmair H, Koletzko B. Fatty acid composition of lipid classes in maternal and cord plasma at birth. Eur J Pediatr. 1998;157:763–8.
66. Desforges M, Sibley CP. Placental nutrient supply and fetal growth. Int J Dev Biol. 2010;54:377–90.
67. Sandovici I, Hoelle K, Angiolini E, et al. Placental adaptations to the maternal-fetal environment: implications for fetal growth and developmental programming. Reprod Biomed Online. 2012;25:68–89.
68. Magnusson AL, Waterman IJ, Wennergren M, et al. Triglyceride hydrolase activities and expression of fatty acid binding proteins in the human placenta in pregnancies complicated by intrauterine growth restriction and diabetes. J Clin Endocrinol Metab. 2004;89:4607–14.
69. Lindegaard ML, Damm P, Mathiesen ER, et al. Placental triglyceride accumulation in maternal type 1 diabetes is associated with increased lipase gene expression. J Lipid Res. 2006;47:2581–8.
70. Barrett HL, Kubala MH, Scholz Romero K, et al. Placental lipases in pregnancies complicated by gestational diabetes mellitus (GDM). PLoS ONE. 2014;9:e104826.
71. Gauster M, Hiden U, van Poppel M, et al. Dysregulation of placental endothelial lipase in obese women with gestational diabetes mellitus. Diabetes. 2011;60:2457–64.
72. Richards MR, Listenberger LL, Kelly AA, et al. Oligomerization of the murine fatty acid transport protein 1. J Biol Chem. 2003;278:10477–83.
73. Bonen A, Chabowski A, Luiken JJ, et al. Is membrane transport of FFA mediated by lipid, protein, or both? Mechanisms and regulation of protein-mediated cellular fatty acid uptake: molecular, biochemical, and physiological evidence. Physiology (Bethesda). 2007;22:15–29.
74. Pohl J, Ring A, Ehehalt R, et al. New concepts of cellular fatty acid uptake: role of fatty acid transport proteins and of caveolae. Proc Nutr Soc. 2004;63:259–62.
75. Grevengoed TJ, Klett EL, Coleman RA. Acyl-CoA metabolism and partitioning. Annu Rev Nutr. 2014;34:1–30.
76. Alvino G, Cozzi V, Radaelli T, et al. Maternal and foetal fatty acid profile in normal and intrauterine growth restriction pregnancies with and without preeclampsia. Pediatr Res. 2008;64:615–20.
77. Tobin KA, Johnsen GM, Staff AC. Long-chain polyunsaturated fatty acid transport across human placental choriocarcinoma (BeWo) cells. Placenta. 2009;30:41–7.
78. Enke U, Seyfarth L, Schleussner E, et al. Impact of PUFA on early immune and foetal development. Br J Nutr. 2008;100:1158–68.
79. Berghaus TM, Demmelmair H, Koletzko B. Essential fatty acids and their long-chain polyunsaturated metabolites in maternal and cord plasma triglycerides during late gestation. Biol Neonate. 2000;77:96–100.

80. Pagan A, Prieto-Sanchez MT, Blanco-Carnero JE, et al. Materno–fetal transfer of docosahexaenoic acid is impaired by gestational diabetes mellitus. Am J Physiol Endocrinol Metab. 2013;305:E826–33.
81. Duttaroy AK. Fatty Acid Uptake and Metabolism in the Human Placenta. In: Duttaroy AK, Basak S, editors. Human Placental Trophoblasts: Impact of Maternal Nutrition. Florida, USA: CRC Press; 2016. p. 85–92.
82. Bobiński R, Mikulska M. The ins and outs of maternal-fetal fatty acid metabolism. Acta Biochim Pol. 2015;62:499–507.
83. Radaelli T, Lepercq J, Varastehpour A, et al. Differential regulation of genes for fetoplacental lipid pathways in pregnancy with gestational and type 1 diabetes mellitus. Am J Obstet Gynecol. 2009;201:209,e1-209,e10.
84. Thomas BA, Ghebremeskel K, Lowy C, et al. Plasma fatty acids of neonates born to mothers with and without gestational diabetes. Prostaglandins Leukot Essent Fatty Acids. 2005;72:335–41.
85. Wijendran V, Bendel RB, Couch SC, et al. Fetal erythrocyte phospholipid polyunsaturated fatty acids are altered in pregnancy complicated with gestational diabetes mellitus. Lipids. 2000;35:927–31.
86. Lappas M. Effect of pre-existing maternal obesity, gestational diabetes and adipokines on the expression of genes involved in lipid metabolism in adipose tissue. Metabolism. 2014;63:250–62.
87. Duttaroy AK, Jorgensen A. Insulin and leptin do not affect fatty acid uptake and metabolism in human placental choriocarcinoma (BeWo) cells. Prostaglandins Leukot Essent Fatty Acids. 2005;72:403–8.
88. Lager S, Jansson N, Olsson AL, et al. Effect of IL-6 and TNF-alpha on fatty acid uptake in cultured human primary trophoblast cells. Placenta. 2011;32:121–7.

Chapter 35
Folic Acid and Gestational Diabetes: Foundations for Further Studies

Elisa Keating, Fátima Martel and João R. Araújo

Key points

- Gestational diabetes has been associated with higher levels of homocysteine and also with qualitative (but not quantitative) changes in folic acid placental transport;
- High folic acid supplementation has been suggested to be associated with increased risk of gestational diabetes;
- Imbalance between vitamin B12 and folate levels seems to be critical for the development of worse metabolic outcomes;
- Folic acid supplementation seems to rescue from poor outcomes induced by gestational diabetes;
- Excessive folic acid supplementation may program the offspring for metabolic dysfunction with first phenotypic alterations occurring in childhood.

Keywords Folic acid · Gestational diabetes mellitus · Placental transporters · Fetal programming · Folic acid supplementation

Abbreviations

5-MTHF	5-methyltetrahydrofolate
BMI	Body mass index
CRH	Cortisol-releasing hormone
DTB	Gestational diabetes-derived tophoblast
FA	Folic acid
GDM	Gestational diabetes mellitus
hPL	Human placental lactogen
HCys	Homocysteine
IADPSG	International Association of Diabetes and Pregnancy Study Group
NTB	Normal trophoblast

E. Keating (✉)
Department of Biochemistry, Faculty of Medicine, CINTESIS, Center for Research in Health Technologies and Information Systems, University of Porto, Al. Prof. Hernâni Monteiro, Porto, Portugal
e-mail: keating@med.up.pt

F. Martel
Department of Biochemistry, Faculty of Medicine, Institute for Research and Innovation in Health Sciences, University of Porto, Al. Prof. Hernâni Monteiro, Porto, Portugal
e-mail: fmartel@med.up.pt

J.R. Araújo
INSERM U1202, Unité de Pathogénie Microbienne Moléculaire, Institut Pasteur, 28, rue du Dr Roux, Cédex 15 Paris France
e-mail: joao.diniz-de-araujo@pasteur.fr

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*, Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_35

NTDs	Neural tube defects
OGTT	Oral glucose tolerance test
SAM	S-adenosylmethionine
STB	Syncytiotrophoblast
TNF-α	Tumor necrosis factor α

Recommendations and guidelines

Specifically, (a) GDM is suggested to be associated with higher HCys levels and also with qualitative changes in FA placental transport; (b) high FA supplementation has been suggested to be associated with increased risk of GDM; (c) optimal FA supplementation seems to rescue from poor outcomes induced by GDM; (d) excessive FA supplementation may program the offspring for metabolic dysfunction with first phenotypic alterations occurring in childhood.

Obstetrical and primary health care clinical practice will certainly profit from increased awareness regarding specifically:

- the impact of excessive folic acid supplementation during pregnancy (above 800 μg per day) on metabolic health of the mother and the offspring
- the ability of adequate (not excessive) folic acid supplementation during pregnancy to rescue from poor outcomes induced by gestational diabetes
- the pertinence of conditional or personalized folic acid supplementation during pregnancy, taking into consideration individual factors such as folate and vitamin B12 plasma levels as well as pre-pregnancy body mass index.

Introduction

Gestational diabetes mellitus (GDM) or simply gestational diabetes corresponds to hyperglycemia resulting from any degree of glucose intolerance, with first detection during pregnancy [1]. In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) has recommended the following GDM diagnostic criteria: attaining or exceeding any of the following plasma glucose thresholds, usually at 24–28 weeks of gestation: 92 mg/dl (5.1 mM) for fasting plasma glucose, 180 mg/dl (10.0 mM) for plasma glucose after 1-h oral glucose tolerance test (OGTT) or 153 mg/dl (8.5 mM) for plasma glucose after 2-h OGTT [2]. These new diagnostic criteria more than doubled the prevalence of GDM to approximately 18% of all pregnancies [3], when compared to the old criteria, which were based on higher glucose thresholds.

Pregnancy is a metabolically demanding and dynamic state. It envisages a progressive physiological decrease in insulin sensitivity (accompanied by an increase in insulin secretion) that ultimately results in the sparing of glucose for the increasing demands of the feto-placental unit [4, 5]. This physiological maternal insulin resistant state is thought to result from the action of the progressively increasing levels of placental diabetogenic hormones or factors such as progesterone, cortisol-releasing hormone (CRH), human placental lactogen (hPL), leptin, or tumor necrosis factor α (TNF-α) [4–8]. However, when insulin secretion by maternal pancreatic β-cells becomes insufficient to compensate for the physiological insulin resistance, GDM develops [4, 5].

Folates are critically important in pregnancy. Firstly, low maternal folate levels increase the risk of low birth weight and of neural tube defects (NTDs) [9], and supplementation with FA during the periconceptional period reduces the incidence of such outcomes [9]. In addition, by conveying methyl units for epigenetic regulation of gene expression, folates are recognized as important players in fetal programming [10].

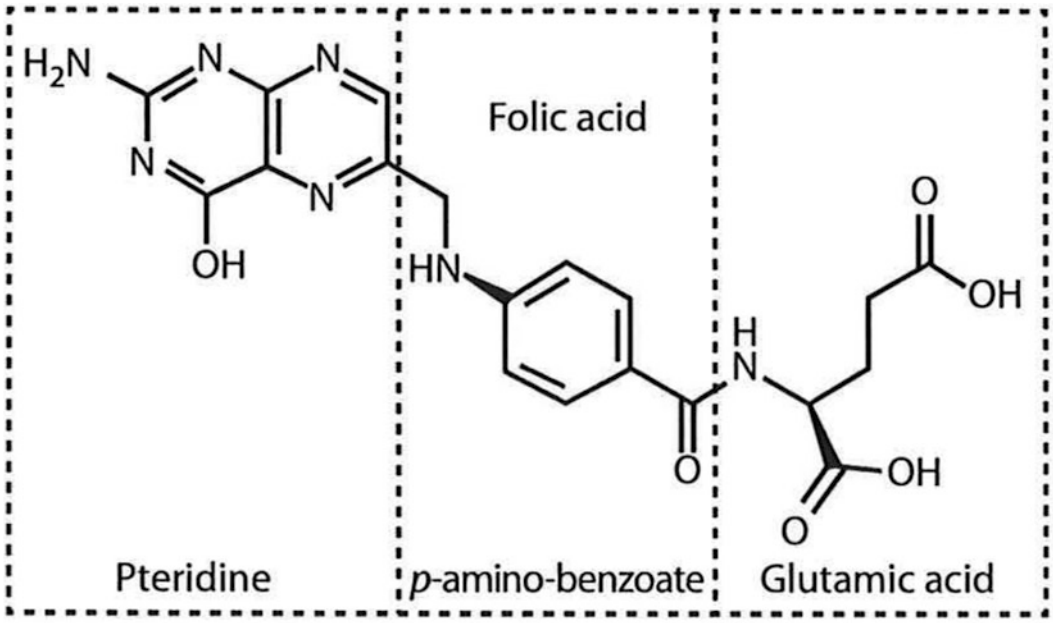


Fig. 35.1 Chemical structure of folic acid

Folic acid (FA, pteroylmonoglutamate) is the synthetic structure of the folate family of water-soluble vitamins (Fig. 35.1). FA may be acquired in the human diet from artificially FA-enriched foodstuffs. On the other hand, reduced folates such as 5-methyltetrahydrofolate (5-MTHF), the main naturally occurring folate form may be found in leafy green vegetables, yeast, liver, and nuts.

At the cellular level folate, one-carbon metabolism, which is schematized in Fig. 35.2, is critical (a) for the production of nitrogen bases which are used for the synthesis of nucleic acids [9] and thus for correct cell division; (b) for the provision of S-adenosylmethionine (SAM), an important substrate for cellular methylation reactions [11]; (c) for the initiation of protein synthesis in the mitochondria, and (d) for the metabolism of several amino acids (L-methionine, L-serine, L-glycine and L-histidine) [9].

So, considering that (a) GDM programs the offspring for metabolic dysfunction later in life [12], (b) folate is an important player in fetal programming [10] and (c) both maternal diabetes [13] and folate deficiency [9] are associated with increased risk of neural tube defects it is plausible to hypothesize that GDM may directly affect the maternal/fetal folate status, thereby inducing lifelong changes in gene expression through epigenetic mechanisms (Fig. 35.3).

In the context of this hypothesis, this chapter will review available evidence of the relationship between alterations in folate metabolism and GDM.

The Impact of GDM on Folate Metabolism

Available literature is parsimonious regarding the impact of GDM on FA metabolism; however, several studies regarding the impact of homocysteine (Hcys) levels in GDM pregnancies or in relation to birthweight have been published (Table 35.1). HCys is a marker of low folate or vitamin B12 status (Fig. 35.2). Indeed, whenever folate or vitamin B12 (or both) are deficient, HCys cellular levels

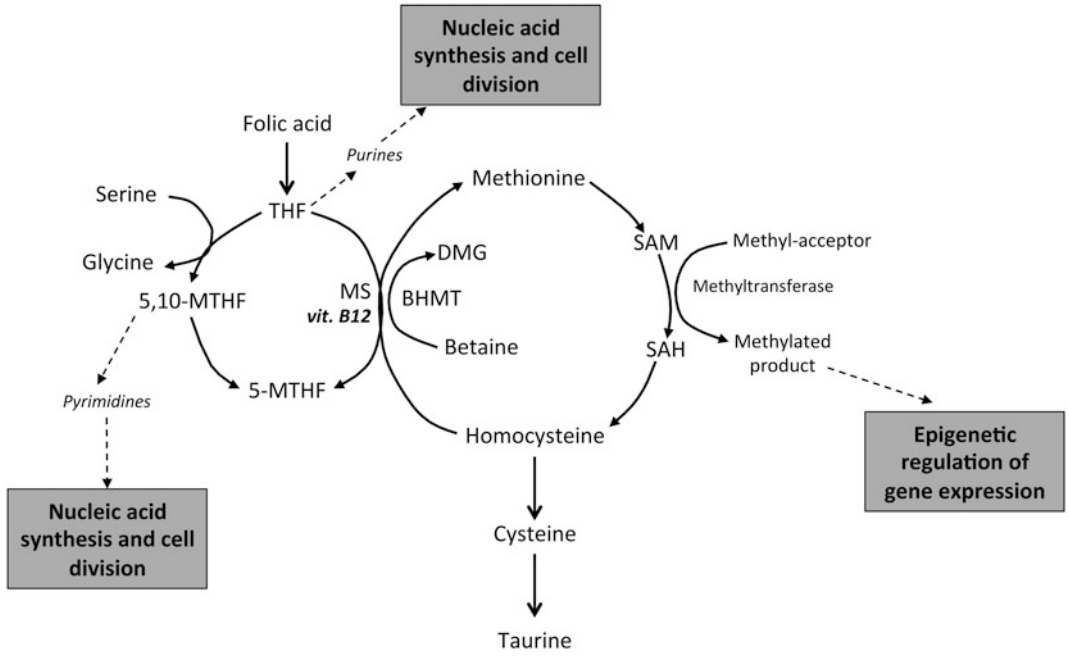


Fig. 35.2 Schematic representation of cellular folate metabolism. *Legend* 5,10-MTHF: N^5, N^{10}-methylenetetrahydrofolate; 5-MTHF: N^5-methyltetrahydrofolate; *BHMT* betaine–homocysteine methyltransferase; *DMG* dimethylglycine; *MS* methionine synthase; *SAH* S-adenosylhomocysteine; *SAM* S-adenosylmethionine; *THF* tetrahydrofolate; *vit B12* vitamin B12

increase and hyperhomocysteinemia arises. Hyperhomocysteinemia has been associated with several diseases such as cancer, diabetes, and cardiovascular disease [14], although the molecular mechanisms implicating homocysteine in the pathophysiology of those diseases is still largely unclear.

Regarding GDM, several studies have found that homocysteine levels are higher in GDM women, when compared to non-diabetic pregnant women [15–17], or are associated with insulin resistance or low birthweight [18, 19]. It is important to note, however, that in the studies where differences in HCys were found in GDM, when compared to glucose-tolerant controls, the levels of blood folate did not differ between groups [15–17, 19], and vitamin B12 levels were found to be lower in GDM in only one of these studies [17]. Moreover, the biological significance of high HCys in GDM remains to be understood (Table 35.1).

It is possible that elevated HCys levels arising in GDM may reflect a defect in one-carbon metabolism which may lead to defects in epigenetic regulation of gene expression. This could underlie the fetal programming effect of GDM. In this context it would be interesting to search for a possible association between HCys levels in pregnancy, genome methylation in the placenta and in the fetus, and the programming of disease later in life.

The Impact of GDM on FA Placental Transport

While GDM does not seem to affect folate levels in pregnant women (albeit it seems to affect HCys levels, see previous section), it still could affect folate supply to the placenta and the fetus.

The human placenta expresses three specific folate transporters, namely the reduced folate carrier (RFC1), the alpha isoform of the folate receptor (FRα) and the proton-coupled folate transporter

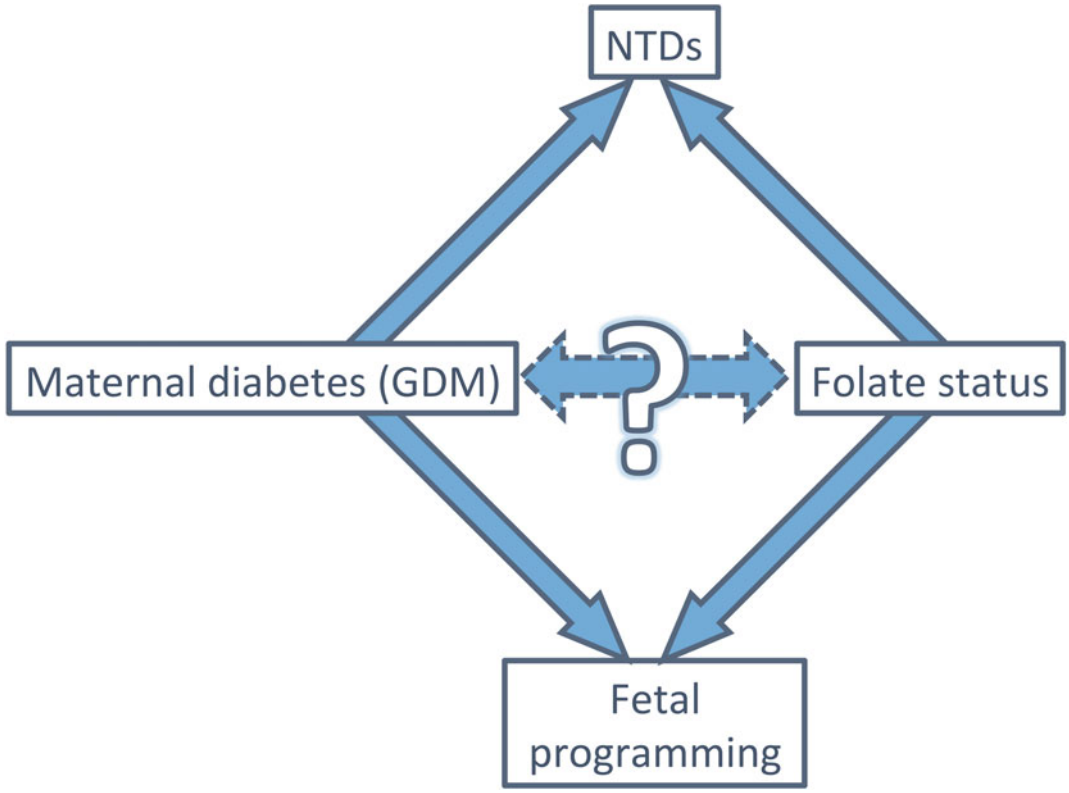


Fig. 35.3 Plausible relationship between GDM and folate status. The hypothesis that GDM may directly affect the maternal/fetal folate status, thereby inducing lifelong changes in gene expression through epigenetic mechanisms, relies on the notions that (**a**) GDM programs the offspring for metabolic dysfunction later in life, (**b**) folate is an important player in fetal programming, and (**c**) both maternal diabetes and folate deficiency are associated with increased risk of neural tube defects (NTDs)

(PCFT). All of them act coordinately to ensure the vectorial transfer of folates from maternal to fetal circulation [20–22] (Fig. 35.4).

RFC1 is a folate: organic phosphate exchanger that utilizes the transmembrane organic phosphate gradient to mediate the uphill transport of folates into cells [22, 23]. This bidirectional transporter is expressed in both MVM and BM of the syncytiotrophobalst (STB) [21] (Fig. 35.4), has a maximal activity at physiological pH, and a higher affinity for reduced folates (such as N^5-methyltetrahydrofolate) over non-reduced folates [22, 23]. FRα is a high-affinity folate-binding protein selectively expressed in the MVM of the STB (Fig. 35.4). PCFT is a high-affinity folate: H^+ symporter, with an optimal activity at acidic pH (5.5–6.0), that utilizes the transmembrane H^+ gradient to achieve the uphill transport of folates into cells [20, 22, 23]. PCFT is predominantly present at the MVM, where it co-localizes with FRα [21] (Fig. 35.4).

Other potential folate transporters localized at the BM and/or MVM of the STB, namely the ATP-binding cassette efflux transporters multidrug resistance-associated proteins and breast cancer resistance protein [23], may also play a role in FA transport but their exact contribution is still poorly understood.

Our group has recently studied the impact of GDM upon FA placental transport [24] in primary cultured human cytotrophoblasts from normal (NTB cells) or GDM (DTB cells) pregnancies. Additionally, we have studied the effect of GDM-associated conditions upon FA uptake by placental cells [24].

Table 35.1 Studies analyzing homocysteine levels in relation to gestational diabetes mellitus or birthweight

Ref	Publication year	Country	Studied population	Sample size	Type of study	Results/main conclusions
[18]	2014	India	Pregnant women and offspring	526 (Pune Maternal Nutrition Study, PMNS) and 515 (Parthenon Cohort Study)	Cohort	Offspring birthweight was inversely related to maternal homocysteine concentration. Data suggest a causal role for maternal homocysteine in fetal growth
[19]	2008	Poland	Pregnant women	44 GDM; 17 controls	Cross-sectional	Serum homocysteine levels were similar in both groups (8 ± 2.0 in GDM versus 7.4 ± 1.1 micromol/l in controls). In GDM: serum homocysteine is significantly associated with vitamin B(12) and folate levels. In controls: serum homocysteine is associated with HOMA-IR and kidney function
[15]	2006	Turkey	Pregnant women	30 GDM; 46 glucose intolerante; 147 normal controls	Cross-sectional	Second trimester serum homocysteine concentrations are higher in GDM, when compared to normal controls. Folate and vitamin B12 levels did not differ between groups
[16]	2004	Turkey	Pregnant women	28 GDM; 66 abnormal 50 g test but normal OGTT; 210 normal controls	Cohort	GDM women and women with abnormal screening test have higher homocysteine levels than normal controls. Folate and vitamin B12 levels did not differ between groups
[17]	2003	Italy	Pregnant women	15 GDM; 78 normal controls	Cohort	Homocysteine is higher (vitamin B12 is lower and folate is unaltered) in GDM. HCys is significantly related to 2-hour OGTT plasma glucose, and unrelated to insulin resistance in these subjects
[51]	2002	Greece	Pregnant women	15 diabetic; 21 controls	Cross-sectional	No difference in maternal homocysteine levels between groups. Serum homocysteine levels are not elevated in women with gestational-onset diabetes

Data from those approaches showed that ^{3}H-FA uptake by NTB and DTB cells exhibit similar kinetics and occurs optimally at an acidic pH. However, a greater pH-dependence was observed in DTB cells for low pH values (5.0–6.0), which may indicate a higher PCFT: RFC1 relative activity in DTB in comparison with NTB cells.

Still in the work by Araújo et al., short (4 h) and particularly long-term (24 h) hyperleptinemia was shown to decrease ^{3}H-FA uptake, and short-term (4 h) exposure to LPS (in concentrations (1–10 μg/ml) known to induce IL-6 and TNF-α secretion by trophoblasts [25]) and high levels of

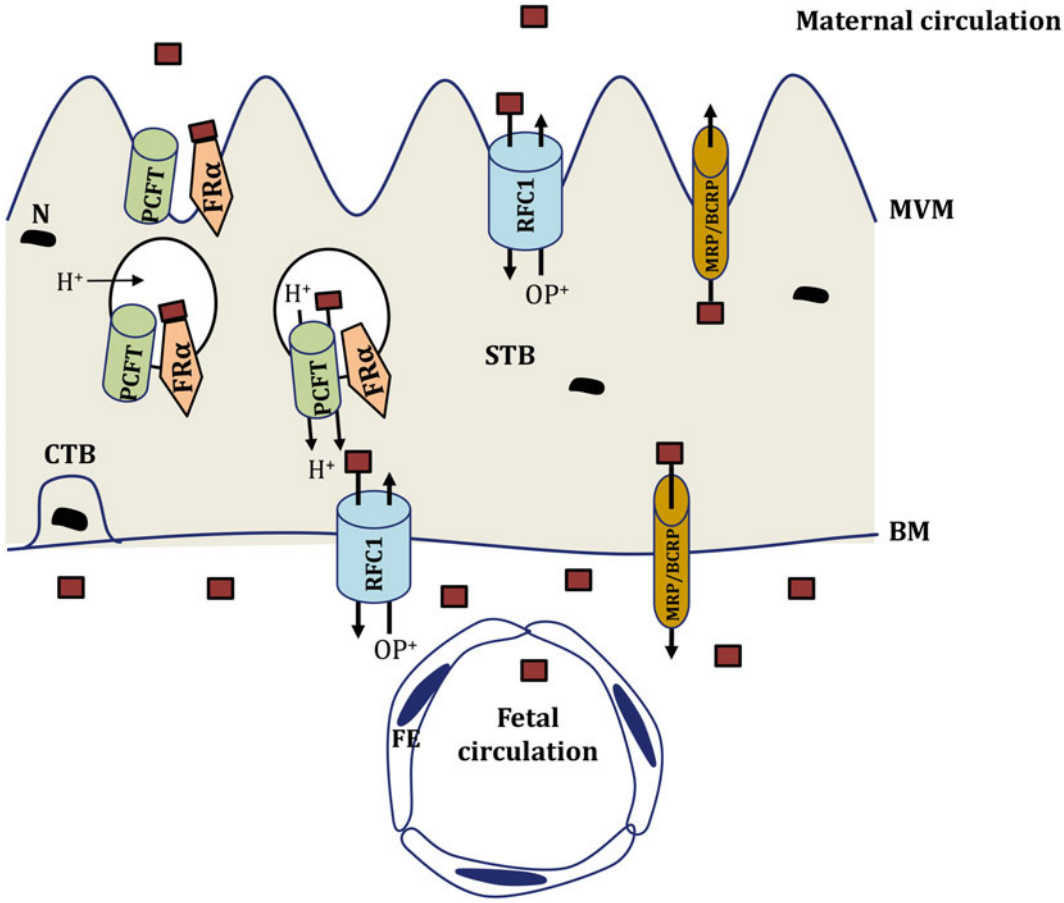


Fig. 35.4 Main folic acid transporters present at the human syncytiotrophoblast. *Legend* ▭ : folic acid; *BM* basal membrane; *CTB* cytotrophoblast; *FRα* folate receptor alpha; *FE* fetal endothelium; *MVM* microvillous membrane; *N* nucleus; *PCFT* proton-coupled folate transporter; *STB* syncytiotrophoblast; *RFC1* reduced folate carrier 1

TNF-α (300 ng/l) itself reduced ^{3}H-FA uptake in BeWo cells. On the other hand, hyperglycemia and hyperinsulinemia were devoid of effect upon ^{3}H-FA uptake.

Leptin has important placental functions including regulation of nutrient metabolism and trophoblast proliferation, invasion, and angiogenesis [26–28], suggesting that this hormone may affect fetal growth [29]. The functions attributed to leptin depend upon its binding to specific receptors, which have been localized in the human STB [27], resulting in activation of the following signal transduction pathways: JAK (janus kinases)/STAT (signal transducers and activators of transcription), PI3K, protein kinases (PK) A and C, and mitogen-activated protein kinases (MAPK) such as extracellular-signal-regulated-kinase (ERK), c-Jun-N-terminal kinase (JNK), and p38 MAPK [27, 30]. Further experiments searching for the intracellular pathways involved in the inhibitory effect of long-term leptin upon ^{3}H-FA uptake in BeWo cells, showed that this effect seemed to be independent of JAK/STAT, PI3 K, PKA, PKC, and MAPK signaling pathways.

Since GDM affects the methylation of genes responsible for fetal growth and energy metabolism at placental level [31], and methylation of RFC1 gene is associated with a lower expression of this transporter [11], it can be speculated that GDM affects FA transport through epigenetic mechanisms.

The Impact of Folic Acid Supplementation in GDM

FA supplementation is one of the most popular nutritional interventions in pregnancy. In the 1990s, two important studies showing that FA supplementation in the periconceptional period was effective in preventing the recurrence and first occurrence of NTDs [32, 33], motivated the formulation of several strategies for FA food fortification and FA supplementation of women in childbearing age. For example, the Food and Drug Administration mandated the fortification of all grain products with FA, in the USA in the late 1990s. At that time it was assumed that folate status was generally inadequate. For example, in Portuguese women, it was estimated that folate inadequacy in the year 2009 was 58.2 and 90.8% in the year before and during pregnancy, respectively [34].

Since the early 1990s, more than 50 countries worldwide implemented mandatory food fortification with FA; of note, among European countries, although some permitted voluntary fortification, none had implemented mandatory fortification given the suspicion of health hazards [35].

In addition to this, at present date, the World Health Organization (WHO) recommends a daily supplementation with 400 μg (in association with 30–60 mg of iron) during pregnancy beginning as early as possible.

FA supply during pregnancy, either as a supplement pill or via food fortification, in low doses and during the periconceptional period has proven to be effective in preventing NTDs. However, all the above referred public health policies, together with the fact that FA pills for supplementation are available in some countries only in unit doses of 5 mg, raise the concern that FA intake may be exceeding the recommended upper levels. Indeed, although FA is a water-soluble vitamin which is expected to be freely excreted in urine, there is evidence that FA intake above the 400 μg recommended daily dose, induces the appearance of unmetabolized FA in blood [36]. Moreover, several recent studies report deleterious effects of excessive FA supplementation for example in neurodevelopment [37], embryonic development [38], or metabolism later in life [39].

Table 35.2 summarizes evidence taken from studies that associated FA supplementation, or methyl-nutrient levels, with outcomes such as GDM. Of these, one very recent cohort study [40] of Chinese pregnant women showed that daily supplementation with FA during the first trimester of pregnancy more than doubled the risk of GDM (adjusted odds ratio 2.25). Importantly, pre-pregnancy overweight women that took daily FA supplements in the first trimester had an even higher risk of GDM, when compared with normal weight women that did not take FA supplements. It was also found that the risk of GDM did not seem to increase with FA supplementation in the second trimester of pregnancy. The authors suggested that this effect of FA may be related to an imbalance between vitamin B12 and folate levels, with possible repercussions in HCys levels and concomitant deterioration of insulin sensitivity. They also raised the hypothesis that the appearance of unmetabolized FA in blood, resulting from high FA supplementation, may underlie the increase in GDM risk, since unmetabolized FA has been associated with reduced natural killer cell cytotoxicity, an event implicated in the pathophysiology of GDM [40]. A weakness of this study, however, is that the dose of FA supplementation is not characterized, and it cannot be ascertained whether it corresponds to an excess of FA or to an optimal-dose FA supplementation.

Another interesting study of a small cohort of 785 Indian pregnant women, reports that vitamin B12 deficiency, particularly when associated with high-folate status, increases the risk of diabesity (adiposity and diabetes) in pregnant women [41]. Although this study is not an intervention trial, vitamin B12 and folate levels were measured in plasma of women in pregnancy and at 5 years follow-up, and it corroborates the relevance of the imbalance between vitamin B12 and folate levels, referred above.

Still regarding vitamin B12, a cross-sectional study by Adaikalakoteswari et al. [42] showed that low maternal vitamin B12 levels were associated with poor metabolic risk markers in the mother, particularly regarding lipid metabolism and with low HDL levels in the neonate. Associations found

Table 35.2 Human studies analyzing the impact of folic acid, or methyl nutrients, on gestational diabetes mellitus

Ref	Publication year	Country	Studied population	Sample size	Type of study	Results/main conclusions
[40]	2016	China	Pregnant women	3744	Cohort	Daily FA supplementation in first trimester was associated with a doubled risk of GDM. Women with a prepregnancy BMI $\geq$ 25 kg/m^2 and taking FA supplements daily in the first trimester had a 5 times higher risk of GDM compared with women with a prepregnancy BMI < 25 kg/m^2 and not taking any FA supplements
[41]	2009	India	Pregnant women	785	Cohort	The risk of GDM was highest among women with B12 deficiency and high-folate concentrations
[43]	2015	China	Pregnant women	7812	Cohort	The complication rates (especially GDM and hypertension) in different age groups were lowered after folic acid supplementation
[42]	2015	UK	Pregnant women and offspring	91	Cross-sectional	Maternal serum vitamin B12 is independently associated with neonatal HDL-cholesterol and homocysteine but not triglycerides or HOMA-IR

between folate levels and metabolic outcomes were weaker, but it was suggested that low folate levels associate also with poor metabolic outcomes. This was, however, a cross-sectional study with a small sample size that cannot by itself demonstrate those independent associations. Nevertheless, this study reinforces the idea that non-optimal concentrations of methyl nutrients may induce metabolic dysfunction in both the mother and the offspring.

Finally, the study of Li et al. [43], in which folate supplementation was assessed, could provide evidence that GDM and gestational hypertension were reduced in all age groups receiving FA supplementation, when compared with matched aged groups of unsupplemented pregnant women. The daily dose of FA referred in this study did not exceed 800 μg and thus it does not correspond to an excessive dose of FA. This study suggests that an optimal supply of FA is indeed health-promoting. A pitfall of this study is that it does not discriminate pregnancy stages for which the effect is observed.

Animal studies exploring the relationship between FA and GDM are summarized in Table 35.3. Globally, these studies show that FA supplementation of diabetic mice ameliorates diabetic pregnancy outcomes such as NTD, cardiovascular and skeletal malformations [44], vascular morphology and apoptotic rate [45], and overall malformation rate [46]. Although the doses of FA are variable among these studies (either recommended or excessive), it is apparent that FA supplementation may rescue from poor diabetic outcomes of pregnancy. It would be interesting to confirm these observations in human studies.

The Long-Term Metabolic Impact of Folic Acid Supplementation

While the relationship between FA supplementation and GDM is still not very clear, the effect of high FA supplementation during the periconceptional/perigestational period in inducing fetal programming of metabolic dysfunction is becoming increasingly accepted. This is concerning for two main reasons: firstly, FA oversupplementation by itself may be feeding metabolic syndrome epidemics. Secondly,

Table 35.3 Animal studies analyzing the relationship between folic acid and gestational diabetes mellitus

Ref	Publication year	Studied population	Sample size	Type of study	Intervention	Results/main conclusions
[44]	2009	Female ICR mice	5–8	Animal study	3 mg FA/Kg body weight or saline to pregnant diabetic mice between gestational days 6 and 10	In the FA-treated diabetic mice, the incidence of NTDs reduced from 28.4 to 6.0%, of cardiovascular malformations from 28.5 to 2.5% and of skeletal malformations from 29.7 to 12.5%. It is concluded that FA prevents from various diabetic embryopathy independently of homocysteine metabolism
[45]	2007	Sprague Dawley pregnant rat (controls and diabetic)	3–5 per experimental group	Animal study	15 mg FA/kg body weight Beginning on gestational day 0 until termination of pregnancy	FA administration normalized vascular morphology, apoptotic rate, Vegf-A gene expression and protein distribution in the yolk sac of diabetic rats
[46]	2005	Sprague Dawley pregnant rat (controls and diabetic)	4–5 per experimental group	Animal study (*in vitro*)	Embryos cultured in high or normal glucose medium were exposed to 0 or 2 mmol/L FA during 48 h	FA supplementation to embryos cultured in diabetic environment decreased malformation rates

since a pregnancy beginning on a poor metabolic status is more prone to result in poor metabolic outcomes for both the mother and the offspring, excess FA, by promoting metabolic dysfunction in female offspring, will exponentially increase the prevalence of metabolic dysfunction and associated diseases such as obesity and diabetes.

Our group has recently observed that excessive FA supplementation of Sprague Dawley rats during the perigestational period (from preconception until the end of lactation) worsens metabolic function particularly of female offspring later in life. Additionally, in this study, high FA supplementation rendered female offspring more prone to develop metabolic dysfunction after a metabolic insult such as chronic fructose feeding [39]. Interestingly, in this study, the mothers also developed diabetes-like symptoms, many weeks after weaning and cessation of FA supplementation [39].

A study by Huang et al. [47] strongly corroborates these findings by showing that the administration of excessive FA to pregnant mice (in the same dose as that used in [39]) worsens the metabolic response to high fat-diet stimulus in adult offspring.

Human studies in an Indian population regarding this same issue have been published. Specifically, higher maternal folate levels during gestation have been associated with higher insulin resistance in the offspring at the age of 6 [48, 49], 9.5, and 13.5 years [50]. Additionally, low vitamin B12 maternal levels have been suggested to exaggerate de risk of insulin resistance on an excessive FA background [48, 49]. Finally, high maternal HCys levels have been claimed to be associated with decreased offspring anthropometric measures and higher glucose levels at the age of 5 and 9.5 years.

So, one-carbon metabolism imbalance during pregnancy, particularly high-folate status (with low vitamin B12) may indeed exert a fetal programming effect for future metabolic dysfunction of the offspring. As a whole, these evidences suggest that excessive FA status during pregnancy may precipitate a worse metabolic performance in the future.

Conclusions

The relationship between FA and GDM, as reviewed in this chapter, is multi-directional and involves multiple players. Not only GDM may influence folate metabolism and delivery to the fetus, involving vitamin B12 and HCys metabolism, but also high-folate levels (excessive supplementation) during pregnancy may impact metabolic health of the mother during pregnancy and/or the offspring later in life.

More specifically, (a) GDM has been associated with higher HCys levels (not necessarily associated with low folate levels) and also with qualitative (but not quantitative) changes in FA placental transport; (b) high FA supplementation has been suggested to be associated with increased risk of GDM, and GDM has been observed to be less frequent in optimal-dose FA supplemented groups of pregnant women; (c) optimal FA supplementation seems to rescue from poor outcomes induced by GDM; and (d) excessive FA supplementation may program the offspring for metabolic dysfunction with first phenotypic alterations occurring in childhood.

It is thus apparent that one-carbon metabolism may be disturbed by GDM with possible implications for cellular methylation, epigenetic regulation of gene expression and thus fetal programming. However, the specific mechanisms underlying these relationships are still underexplored.

Research themes that deserve additional efforts include:

- The relationship between homocysteine levels in pregnancy, fetal genome methylation, and fetal programming
- The putative impact of gestational diabetes on epigenetic regulation that may impact folate placental transport
- The role of the imbalance between folic acid and vitamin B12 levels on the risk of dysmetabolism in the pregnant woman and her offspring.

These research efforts will certainly contribute for a deeper knowledge and increased awareness on the importance of the theme, and thus for the improvement of metabolic health outcomes of mothers and their offspring.

References

1. ADA. Diagnosis and classification of diabetes mellitus. Diab Care. 2013;36(Suppl 1):S67–74.
2. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care. 2010;33(3):676–82.
3. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diab Care. 2012;35(3):526–8.
4. Baz B, Riveline J-P, Gautier J-F. Endocrinology of pregnancy: gestational diabetes mellitus: definition, aetiological and clinical aspects. Eur J Endocrinol. 2016;174(2):R43–51.
5. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: a clinical update. World J Diab. 2015;6(8):1065–72.
6. Golbidi S, Laher I. Potential mechanisms of exercise in gestational diabetes. J Nutr Metab. 2013;2013:285948.

7. Vargas R, Repke JT, Ural SH. Type 1 diabetes mellitus and pregnancy. Rev Obstet Gynecol. 2010;3(3):92–100.
8. Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50(4):938–48.
9. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000;71(1–2):121–38.
10. Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. Annu Rev Nutr. 2010;30:315–39.
11. Farkas SA, Bottiger AK, Isaksson HS, Finnell RH, Ren A, Nilsson TK. Epigenetic alterations in folate transport genes in placental tissue from fetuses with neural tube defects and in leukocytes from subjects with hyperhomocysteinemia. Epigenetics. 2013;8(3):303–16.
12. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diab Care. 2007;30(Suppl 2):S251–60.
13. Salbaum JM, Kappen C. Neural tube defect genes and maternal diabetes during pregnancy. Birth Defects Res A Clin Mol Teratol. 2010;88(8):601–11.
14. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015;14:6.
15. Guven MA, Kilinc M, Batukan C, Ekerbicer HC, Aksu T. Elevated second trimester serum homocysteine levels in women with gestational diabetes mellitus. Arch Gynecol Obstet. 2006;274(6):333–7.
16. Tarim E, Bagis T, Kilicdag E, Erkanli S, Aslan E, Sezgin N, et al. Elevated plasma homocysteine levels in gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2004;83(6):543–7.
17. Seghieri G, Breschi MC, Anichini R, De Bellis A, Alviggi L, Maida I, et al. Serum homocysteine levels are increased in women with gestational diabetes mellitus. Metabolism. 2003;52(6):720–3.
18. Yajnik CS, Chandak GR, Joglekar C, Katre P, Bhat DS, Singh SN, et al. Maternal homocysteine in pregnancy and offspring birthweight: epidemiological associations and Mendelian randomization analysis. Int J Epidemiol. 2014;43(5):1487–97.
19. Idzior-Walus B, Cyganek K, Sztefko K, Seghieri G, Breschi MC, Walus-Miarka M, et al. Total plasma homocysteine correlates in women with gestational diabetes. Arch Gynecol Obstet. 2008;278(4):309–13.
20. Keating E, Goncalves P, Campos I, Costa F, Martel F. Folic acid uptake by the human syncytiotrophoblast: interference by pharmacotherapy, drugs of abuse and pathological conditions. Reprod Toxicol. 2009;28(4):511–20.
21. Solanky N, Requena Jimenez A, D'Souza SW, Sibley CP, Glazier JD. Expression of folate transporters in human placenta and implications for homocysteine metabolism. Placenta. 2010;31(2):134–43.
22. Zhao R, Matherly LH, Goldman ID. Membrane transporters and folate homeostasis: intestinal absorption and transport into systemic compartments and tissues. Expert Rev Mol Med. 2009;11:e4.
23. Zhao R, Diop-Bove N, Visentin M, Goldman ID. Mechanisms of membrane transport of folates into cells and across epithelia. Annu Rev Nutr. 2011;31:177–201.
24. Araujo JR, Correia-Branco A, Moreira L, Ramalho C, Martel F, Keating E. Folic acid uptake by the human syncytiotrophoblast is affected by gestational diabetes, hyperleptinemia, and TNF-alpha. Pediatr Res. 2013;73(4 Pt 1):388–94.
25. Torricelli M, Voltolini C, Bloise E, Biliotti G, Giovannelli A, De Bonis M, et al. Urocortin increases IL-4 and IL-10 secretion and reverses LPS-induced TNF-alpha release from human trophoblast primary cells. Am J Reprod Immunol. 2009;62(4):224–31.
26. Mouzaki A, Panagoulias I, Raptis G, Farri-Kostopoulou E. Cord blood leptin levels of healthy neonates are associated with IFN-gamma production by cord blood T-cells. PLoS One. 2012;7(7):e40830.
27. von Versen-Hoynck F, Rajakumar A, Parrott MS, Powers RW. Leptin affects system A amino acid transport activity in the human placenta: evidence for STAT3 dependent mechanisms. Placenta. 2009;30(4):361–7.
28. White V, Gonzalez E, Capobianco E, Pustovrh C, Sonez C, Romanini MC, et al. Modulatory effect of leptin on nitric oxide production and lipid metabolism in term placental tissues from control and streptozotocin-induced diabetic rats. Reprod Fertil Dev. 2004;16(3):363–72.
29. D'Ippolito S, Tersigni C, Scambia G, Di Simone N. Adipokines, an adipose tissue and placental product with biological functions during pregnancy. BioFactors. 2012;38(1):14–23.
30. Fruhbeck G. Intracellular signalling pathways activated by leptin. Biochem J. 2006;393(Pt 1):7–20.
31. Lehnen H, Zechner U, Haaf T. Epigenetics of gestational diabetes mellitus and offspring health: the time for action is in early stages of life. Mol Hum Reprod. 2013;19(7):415–22.
32. Wald N, Sneddon J. Prevention of neural tube defects: results of the medical research council vitamin study. MRC vitamin study research group. Lancet. 1991;338(8760):131–7.
33. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832–5.
34. Pinto E, Barros H, dos Santos Silva I. Dietary intake and nutritional adequacy prior to conception and during pregnancy: a follow-up study in the north of Portugal. Public Health Nutr. 2009;12(7):922–31.
35. Keating E, Araujo JR, Martel F. Folic acid uptake and its regulation in the placenta. In: Duttaroy AK, Basak S, editors. Human placental trophoblast: impact of maternal nutrition. USA: CRC press, Taylor & Francis group; 2016.

36. Brown RD, Langshaw MR, Uhr EJ, Gibson JN, Joshua DE. The impact of mandatory fortification of flour with folic acid on the blood folate levels of an Australian population. Med J Aust. 2011;194(2):65–7.
37. Roy S, Kale A, Dangat K, Sable P, Kulkarni A, Joshi S. Maternal micronutrients (folic acid and vitamin B(12)) and omega 3 fatty acids: implications for neuro developmental risk in the rat offspring. Brain Dev. 2012;34(1):64–71.
38. Mikael LG, Deng L, Paul L, Selhub J, Rozen R. Moderately high intake of folic acid has a negative impact on mouse embryonic development. Birth Defects Res A Clin Mol Teratol. 2013;97(1):47–52.
39. Keating E, Correia-Branco A, Araujo JR, Meireles M, Fernandes R, Guardao L, et al. Excess perigestational folic acid exposure induces metabolic dysfunction in post-natal life. J Endocrinol. 2015;224(3):245–59.
40. Zhu B, Ge X, Huang K, Mao L, Yan S, Xu Y, et al. Folic Acid supplement intake in early pregnancy increases risk of gestational diabetes mellitus: evidence from a prospective cohort study. Diab Care. 2016;39(3):e36–7.
41. Krishnaveni GV, Hill JC, Veena SR, Bhat DS, Wills AK, Karat CL, et al. Low plasma vitamin B12 in pregnancy is associated with gestational 'diabesity' and later diabetes. Diabetologia. 2009;52(11):2350–8.
42. Adaikalakoteswari A, Vatish M, Lawson A, Wood C, Sivakumar K, McTernan PG, et al. Low maternal vitamin B12 status is associated with lower cord blood HDL cholesterol in white caucasians living in the UK. Nutrients. 2015;7(4):2401–14.
43. Li X, Jiang J, Xu M, Xu M, Yang Y, Lu W, et al. Individualized supplementation of folic acid according to polymorphisms of methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR) reduced pregnant complications. Gynecol Obstet Invest. 2015;79(2):107–12.
44. Oyama K, Sugimura Y, Murase T, Uchida A, Hayasaka S, Oiso Y, et al. Folic acid prevents congenital malformations in the offspring of diabetic mice. Endocr J. 2009;56(1):29–37.
45. Zabihi S, Eriksson UJ, Wentzel P. Folic acid supplementation affects ROS scavenging enzymes, enhances Vegf-A, and diminishes apoptotic state in yolk sacs of embryos of diabetic rats. Reprod Toxicol. 2007;23(4):486–98.
46. Wentzel P, Eriksson UJ. A diabetes-like environment increases malformation rate and diminishes prostaglandin E (2) in rat embryos: reversal by administration of vitamin E and folic acid. Birth Defects Res A Clin Mol Teratol. 2005;73(7):506–11.
47. Huang Y, He Y, Sun X, He Y, Li Y, Sun C. Maternal high folic acid supplement promotes glucose intolerance and insulin resistance in male mouse offspring fed a high-fat diet. Int J Mol Sci. 2014;15(4):6298–313.
48. Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher DJ, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune maternal nutrition study. Diabetologia. 2008;51 (1):29–38.
49. Deshmukh U, Katre P, Yajnik CS. Influence of maternal vitamin B12 and folate on growth and insulin resistance in the offspring. Nestle Nutr Inst Workshop Ser. 2013;74:145–54; discussion 54–6.
50. Krishnaveni GV, Veena SR, Karat SC, Yajnik CS, Fall CH. Association between maternal folate concentrations during pregnancy and insulin resistance in Indian children. Diabetologia. 2014;57(1):110–21.
51. Vitoratos N, Kassanos D, Salamalekis E, Siristatidis C, Baimacou E, Creatsas G. Maternal homocysteine levels and plasma lipids in gestational diabetes: is there any relationship? J Obstet Gynaecol. 2002;22(4):366–9.

Chapter 36
Iron and Oxidative Stress in Gestational Diabetes

Isabelle Hininger-Favier, Jean-Marc Moulis and Jean-Marc Ayoubi

Key Points

- High iron markers correlate with GDM risk and Type 2 diabetes.
- Although iron stores during pregnancy are essential in preventing negative outcomes for both infants and mothers, they might also increase the risk of GDM. Therefore, the need for iron during pregnancy is a delicate balance.
- oxidative stress (OS) is elevated in pregnant women with GDM.
- Iron intake, in particular haem iron, and moderately elevated ferritin can generate OS and glucose impairment and should be considered at early pregnancy as predictive factors of glucose impairment and risk of GDM.
- The routine of determining ferritin levels to support iron supplementation should be modified for a new clinical practice identifying and preventing GDM in high-risk women.
- Dietary advice, based on the predictive value of ferritin levels at early pregnancy (initial prenatal visit) for risk of GDM, is warranted for high-risk women to reduce the undesirable effects for both mother and child.

Keywords Iron · Oxidative stress · Gestational diabetes mellitus · High iron markers · Type 2 diabetes

Abbreviations

CDC	Centers for disease control and prevention
CRP	C-reactive protein
GDM	Gestational diabetes mellitus
OS	Oxidative stress

I. Hininger-Favier (✉) · J.-M. Moulis
Department of Biology and Nutrition, Faculty of Pharmacy , INSERM U1055, Laboratory of Fundamental and Applied Bioenergetics (LBFA), Université Grenoble Alpes, Grenoble, France
e-mail: isabelle.hininger@univ-grenoble-alpes.fr

J.-M. Moulis
Bioscience and Biotechnology Institute (BIG), CEA, Grenoble, France
e-mail: jean-marc.moulis@cea.fr

J.-M. Ayoubi
Department of Gynecology and Obstetrics, Hôpital Foch, Suresnes, France
e-mail: jm.ayoubi@hopital-foch.org

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_36

T2D Type 2 diabetes
WHO World Health Organization
TBARS Thiobarbituric acid-reactive substances

Introduction

Gestational Diabetes Mellitus (GDM), an important class of diabetes that occurs or is first diagnosed during pregnancy [1], has severely increased over the last 10 years and is now paralleling the obesity and T2D surge. Due to the increased prevalence of GDM throughout the world, GDM is now considered to be a public health concern. Since the International Association of Diabetes and Pregnancy Study Groups (IADPSG) have proposed new criteria, which have also been adopted by WHO [2], GDM is now one of the most frequent pregnancy complications with a prevalence of nearly 14% on average with the new criteria of GDM screening [3], but with likely far higher prevalence in some countries.

As the majority of cases return to normal glycaemic levels postpartum, GDM has, until now, been considered a 'transient condition'. However, evidence suggests that GDM should be viewed more as a marker for chronic disease as mothers age [4]. Indeed, GDM leads not only to short-term but also to long-term adverse health outcomes such as the subsequent development of Type 2 diabetes (T2D) in the mother: this may occur in more than 20% of some populations. There are also convincing data for long-term health outcomes in infancy including glucose intolerance, childhood obesity, decreased intellectual achievement and T2D [5]. A study revealed that almost half of the diabetes cases (47.2%) in any young population can be attributed to maternal GDM [6]. Despite the better diagnosis of GDM and recognition of its adverse consequences for mother and baby in many countries, there is still no consensus regarding the origin of GDM [7].

Taking into account the long-term consequences, including the increased risk of T2D in mothers and newborns, it is essential to identify further risk factors; in particular those influencing glucose metabolism. In particular, pinpointing modifiable factors of GDM may play an important role in prevention and early management of this common pregnancy complication in high-risk populations.

The main risk factors associated with GDM are well-documented [2], and they include the advanced age at pregnancy, now a common element correlating with the evolution of the family concept in many societies. Obesity, ethnicity (Asian, Hispanic, African-Caribbean), family history of diabetes, previous history of GDM, previous macrosomic baby and twin pregnancy are also risk factors for GDM. Moreover, factors that contribute to insulin resistance or relative insulin deficiency both before and during pregnancy may be risk factors for GDM. Besides these well-documented factors, increasing evidence suggests that iron, as a strong pro-oxidant, influences glucose metabolism and may thus be an additional risk factor for GDM [7, 8]. Although iron is an essential nutrient for healthy pregnancy, iron is also an element of conflicting effect since it can be either beneficial or detrimental depending on whether it serves as a micronutrient or as a catalyst of free radical formation. Thus, excess iron leading to oxidative stress may adversely affect maternal and foetal health [8], including the development of gestational diabetes mellitus (GDM). Therefore, while anaemia compromises cognitive development and growth of the newborn, and justifies iron supplementation, the association between iron deficiency without anaemia and adverse perinatal events is less clear.

The objective of this review is to present the current state of knowledge of body iron status assessment during pregnancy, and whether it could be involved in the development of GDM with focus on the potential role of OS induced by iron in the generation and progression of this disease.

Iron supplementation during pregnancy, to mothers who are deemed to be anaemic, has proven to benefit both mother and child and it does not need to be reevaluated. Therefore this scientific point will not be discussed here.

Iron and Pregnancy: A Delicate Balance Between Deficiency and Excess

The total iron needed during pregnancy is estimated at nearly 1.24 g of Fe, for foetal and placental development, red blood cell expansion and compensation for blood loss during delivery. Iron requirements vary during each trimester of pregnancy; decreasing during the first trimester due to cessation of menses, iron requirements begin to rise during the second trimester and as pregnancy progresses, iron requirements for foetal growth rise steadily in proportion to the weight of the foetus, with most of the iron needs accumulating during the third trimester [3].

Screening anaemia in pregnancy: anaemia is defined as haemoglobin <110 g/l at any stage of pregnancy. Currently, there are no recommendations as to the use of different haemoglobin cut-off points for anaemia by trimester, but it is recognized that during the second trimester of pregnancy, haemoglobin concentrations diminish by approximately 5 g/l. According to the US Center for Disease Control (CDC) and Prevention [9] and WHO [17] recommendations, the diagnosis of anaemia during pregnancy must be based on haemoglobin (Hb) values lower than 110 g/l during the first and the third trimester or lower than 105 g/l during the second trimester. WHO and CDC [10] jointly established that Hb and serum ferritin are the two major determinants of iron nutritional status and that a ferritin level <20 μg/l is a marker of a low store level for pregnancy that should conduce to a low iron supplementation if haemoglobin is normal; It is worth noting that in 2011 the WHO report [11] did not propose a cut-off value for the ferritin level during pregnancy because "*Serum ferritin is of limited usefulness in diagnosing iron deficiency during pregnancy, as concentrations fall during late pregnancy, even when bone marrow iron is present*".

Since iron deficiency is one of the most common nutritional disorders in the world, many of the health organizations recommend 30 mg/day of iron during pregnancy. There are three possible ways to prevent and control the development of iron deficiency and iron deficiency anaemia. These encompass dietary diversification, food fortification and individual supplementation. The most commonly prescribed treatments are orally administered. The routine use of iron prophylaxis during pregnancy is a subject of debate; some health organizations advocate routine iron treatment throughout pregnancy [the CDC, WHO [12] and the International Food Information Council Foundation (http://www.ific.org)], while others recommend a supplementation only at the second and third trimester [13], and still others, such as the Institute of Medicine [14] do not recommend that iron supplements are given to non anaemic women.

Nevertheless getting 30 mg/day only by food during pregnancy is unrealistic considering that the average iron content in a meal is around 6.6 mg/1000 kcal [15]: this means that a pregnant woman must eat more than 4000 kcal to meet the recommendation. However, the iron recommendation is based only on the estimated iron need, and it does not take into account the evidence both of the increased iron absorption and of placental iron transfer during pregnancy. To fulfil the increased iron need, iron absorption is tightly regulated according to body iron reserves, and the increase in iron absorption is largely elicited by a low iron status. In the French study EPIFER, although more than 90% of women did not reach the recommended iron intake, fewer than 4% of them were anaemic [15] supporting the high adaptation of iron metabolism to low intake. During pregnancy, studies using stable iron isotopes consistently show that iron absorption increases with increasing length of gestation from around 8 to 66% [16]. Furthermore the latest finding about iron transfer from the mother to the foetus through the placenta supports that the degree of foetal iron deficiency (ID) is not always as severe as maternal ID [17]. At the maternal-placental interface placental syncytiotrophoblasts acquire ferric iron bound to maternal transferrin at the apical membrane through transferrin receptor 1 [18, 19] which is noticeably up-regulated in pregnant women with ID and IDA [18]. Most foetal iron transfer occurs after the 30th week of gestation, also involving placental expression of hepcidin and ferroportin (Fpn) [19] two proteins known to modulate systemic iron homeostasis in adults. Maternal hepcidin and Fpn synthesis are regulated by changes in iron status and iron requirements, and by

inflammatory cytokines, in particular IL6, which also down-regulates the Fpn gene in placental syncytiotrophoblasts [20].

Taken as a whole, these data support that the compensatory effects of bioavailability could have been underestimated in the recommendation of 30 mg/d of iron intake during pregnancy.

Nevertheless, due to the fact that many epidemiological studies with dietary surveys have shown that women [13] have lower iron intake than the recommendation and also that they do not significantly change dietary habits when they become pregnant, iron supplementation is often prescribed. This medical care has also been supported by the fact that many studies in the past have been carried out in populations at high risk of iron deficiency and of anaemia whereas few took place in countries with high incomes [21, 22]. In these western countries iron supplementation is often proposed during pregnancy depending on the ferritin level [13]. Based on the fact that the serum ferritin concentration is currently considered to be a reliable noninvasive marker of the iron status in pregnancy and postpartum [23], most of these studies have concluded that there is an interest in supplementing iron according to the ferritin and increased haemoglobin levels [24–26]. However, in women with normal haemoglobin and replete iron stores, the placebo and the iron supplementation groups shared a similar iron status [26]. Furthermore, the relationship between the ferritin criterion in the low range and clinical effects is uncertain. Indeed, among the studies that described improvement of the maternal Fe stores and of the haematological parameters under Fe supplementation during pregnancy, few have followed the status of the infants born from these mothers. It is worth noting and it should be stressed that the mean haemoglobin level of the placebo group in all these studies were in the normal range according to the criteria of WHO [11] while the Hb of the iron-supplemented group rose to over 12.5 g/l.

A recent meta-analysis concluded that routine iron supplementation increased the likeliness of haemoglobin levels reaching over 130 g/L [27]. This threshold for Hb levels has been associated with undesirable effects at the highest end of the U-shaped progression of the Hb level; A low birth weight and a high risk of GDM have been reported in cases of high haemoglobin and ferritin levels [28]. In this meta-analysis [27] no evidence of significant clinical effect of routine supplementation on foetus outcomes was observed.

Thus, in agreement with the US Preventive Services Task Force [14] and despite evidence supporting the effectiveness of routine iron supplementation during pregnancy for improving maternal haematological indexes, the clinical significance for both pregnant women and infants remains unclear.

To summarize the data relating iron needs and pregnancy, many studies evaluated the haematological parameters defining anaemia, but few analyzed the clinical consequences. Haemoglobin and ferritin concentration appear as the most convenient screening tests, although future options should follow recent advances in understanding iron homeostasis.

The Clinical Consequences of Suspected Iron Deficiency Without Anaemia, Assessed by a Low Ferritin Concentration but with Normal Haemoglobin Values, Are Unknown

Iron Status and Gestational Diabetes: Epidemiological Evidence

An increasing body of evidence supports that iron accumulation is associated with an increased risk of T2D [29, 30] and its complications [31, 32]. A recent meta-analysis has confirmed an independent and positive association between high levels of serum ferritin and the occurrence of metabolic syndrome, a significant risk factor of T2D [33]. Red-meat intake and ferritin levels have also been associated with an increased risk of T2D in women [34].

Therefore the Question Which Arises Is: Could Iron Be a Risk Factor of GDM?

The first association between serum ferritin levels and gestational glucose intolerance was reported in 1997 [35]. At that time, several studies evaluated the link between iron stores during the first trimester of pregnancy and GDM. In Asian populations high levels of Hb increase the risk of GDM [36]. In a prospective study, Hb or ferritin serum value above 12.2 g/dL and 19.7 μg/L, respectively, were identified as factors for increased GDM in the first trimester of pregnancy [37]. Another study supported the hypothesis that high maternal Hb (more than 13 g/dL) at the initial prenatal visit is an independent risk factor for GDM [odds ratio 1.73 (95% CI 1.08-2.78)] [38], whereas women with iron-deficiency anaemia were reported to have a reduced risk of GDM [39]. In a study in Lebanon we showed that ferritin levels above 40 ng/ml in the first trimester were associated with an increased risk of GDM [40]. Such a result was also reported by others [41], with an increased risk of gestational diabetes associated with high levels of ferritin, of serum iron and of dietary haem iron intake. Therefore both the level of ferritin and the trimester at which it is measured could be important determinants of GDM, and variations of the time of ferritin measurement might explain some discrepancies in the literature.

A recent meta-analysis confirmed that increased ferritin levels were significantly correlated with higher risk of GDM [42]. The comparison between the highest and the lowest serum ferritin levels revealed pooled RR of 1.53 (95% CI: 1.17–2.00)

Thus, pregnant women with a ferritin level above 40 ng/ml at the first trimester should benefit from a specific early care regarding the risk of developing gestational diabetes. It is worth noting that most scientific and medical societies support early screening of GDM rather than postponing it to week 24–28 [43]. This screening should include measurements of ferritin and other iron parameters.

On the other hand, epidemiological studies were conducted in order to investigate whether iron supplementation during pregnancy to increase iron stores may increase the risk of developing GDM. A randomized placebo-controlled trial including 1165 pregnant women concluded that early iron supplementation for at least 12 weeks did not increase the risk of GDM: on the contrary, it may have been beneficial in terms of pregnancy outcomes [44]. However, a case-control study including 500 women with GDM positively associated iron supplementation for at least 2 weeks during mid-pregnancy with a 2–3 fold higher risk of GDM (70.8% iron supplemented vs. 44.4% not supplemented) [45]. A prospective cohort study on 399 pregnant women with increased risk of GDM suggested that high iron intake during pregnancy increased the risk of GDM, especially in women who were not anaemic in early pregnancy [46]. Last, in a prospective study in non-iron supplemented women, we found a positive association between ferritin (>38 μg/l) at early and mid-pregnancy and glucose intolerance in middle-pregnancy, with a greater risk of GDM [40].

It is worth noting that C-reactive protein (CRP) was independent of the correlation between ferritin and GDM, thus dismissing the involvement of inflammation in triggering GDM. Iron excess has also been related to an increase in insulin resistance and β-cells dysfunction in the development of diabetes [47].

The relative risk for GDM in the above mentioned meta-analysis [42] was 3.22 (95% CI:1,73–6.00) for prospective cohort studies between the highest and lowest ferritin levels, and serum ferritin was markedly higher in the case groups than in the control ones.

Taken as a whole, there are convincing data in favour of a positive link between a high ferritin level and the risk of GDM, suggesting that moderately increased ferritin levels may be considered as a risk marker for GDM, and that it may be useful for screening populations at high risk of GDM.

Haem Iron Versus Non-haem Iron Intake in GDM

Iron intake occurs via haem iron, which is obtained from animal sources, and via non-haem iron found in cereals, vegetables, fruits, grains and dairy products. Although animal sources represent only

10–15% of dietary iron on average, haem iron may account for nearly one third of absorbed iron because intestinal uptake is poorly regulated. Non-haem iron is more largely present in human dietary intake, but it is relatively insoluble, it is subjected to interference for intestinal absorption, and it is stringently regulated. Thus, any defect in non-haem iron provision or in the absorption mechanism plays a major role in the increased risk of anaemia, in particular during pregnancy in countries where meat is a minor component of the diet.

A few studies have separately examined the relationship between haem and non-haem iron intake and GDM. In some studies, e.g. [48], only haem iron was associated with an increased risk of GDM: an over three-fold increase in risk of GDM was estimated for women reporting the highest haem iron intake compared to those reporting the lowest. Interestingly the Boston University Slone Epidemiology Birth Defects Study [49] including 7229 participants has studied both the period of iron intake and the ingested iron species, and it showed that, whereas preconceptional high dietary haem iron was associated with an elevated risk of GDM, preconceptional non-haem iron intake from food and from supplements was associated with a decreased risk of GDM. During the preconception period the reduction in the risk of GDM was at least 50% among women who consumed the highest amounts of dietary non-haem iron compared to those who consumed the lowest amounts. Bowers et al. [48] studied 3475 participants in the Nurses' Health Study II cohort, and they observed no multivariable association between non-haem iron and the GDM risk. Intake in non-haem iron might be a marker of healthy dietary pattern, like a «prudent» behaviour or compliance with a Mediterranean diet containing higher amounts of vegetables, legumes, fruits and poultry and more healthy fat. Thus, the balance between the average bioavailability of dietary iron and the overall actions of inhibitors and enhancers of iron absorption may lead to lower iron stores in people consuming a Mediterranean diet [50]. Both of these dietary habits have been associated with a lower risk of GDM compared to a "Westernized" diet rich in red and processed meat and saturated fat [51]. Therefore we cannot exclude that the pattern more than the non-haem iron intake per se explains the link between non-haem iron intake and decreased GDM.

Two other studies have also reported an increased risk of GDM associated with total iron intake [28, 46], but, unlike those previously mentioned, these studies did not fully control the haem and non-haem iron pattern in food, nor potential confounders, such as lipids associated with red and processed meats, which may both have deleterious effects on insulin sensitivity and β cell function [52].

The results from studies of the relationship between intake of iron supplements and GDM have been inconsistent [36, 37, 39, 44, 53]. Two randomized trials examining this relationship have found no evidence of an association: this could be explained by the fact that iron was proposed to anaemic women who were not subject to iron overload and increased ferritin levels. One might also assume that supplements generally contain non-haem iron, which could play a part in the outcome, but further investigations are warranted to properly examine this question.

Thus the form of iron might play a crucial role in the risk of GDM. Further large studies are warranted to strengthen the reliability of the safety and health benefits of non-haem iron intake and iron supplements instead of haem iron, as well as the intake period during pregnancy. This would be helpful to establish more accurate guidelines about iron intake recommendations during pregnancy.

Oxidative Stress, Iron and GDM

During pregnancy, progressive insulin resistance due to maternal adiposity and placental hormones is normally detected between 24 and 28 weeks in the mother to direct the glucose supply to the foetus. For most women, the insulin resistance can be compensated for by elevated insulin secretion from

pancreatic β-cells. However, chronic β-cell dysfunction may take place in some women with the development of GDM. The mechanisms causing β-cell impediment are not clear. Aside from the potential numerous contributing factors such as autoimmune defects, genetic abnormalities or insulin resistance [4], iron induced oxidative stress is a biologically plausible cause, though the mechanisms underlying this association are not fully understood.

Oxidative stress is defined as the imbalance between antioxidants, represented by scavengers of reactive molecules and enzymatic antioxidant defence, and the oxidative environment due to free radical species and oxidative damage, with pre-eminence of the latter. Through Fenton-like reactions (ferrous iron reduction of biological oxidants) iron can generate reactive oxygen or nitrogen species leading to OS. Oxidative injury to phospholipids of organelle membranes is a potential unifying mechanism underlying most theories of iron overload damage [54]. Increased oxidative damage induced by iron as proxidant might decrease insulin withdrawal and metabolism in the liver, which could lead to hyperinsulinemia and T2DM [55]. It has been previously reported that iron overload is associated with iron accumulation in various tissues including liver and pancreas [56]. Furthermore β-cells have been described as being particularly susceptible to oxidative damage, due to their poor antioxidant content, which favours apoptosis and impaired insulin synthesis and secretion [57]. Iron-linked OS may thus contribute to β-cell dysfunction and insulin resistance even in the absence of significant iron overload [32]. The toxic effects of excessive iron accumulation involve cell apoptosis or necrosis or ferroptosis in pancreas and other organs as a consequence of the formation of highly reactive free radicals [29, 56].

Conversely the degree of OS decreases after iron levels are restored by phlebotomy in patients suffering of type I hereditary haemochromatosis [58], a disease associated with an increased risk of T2D. Interestingly paralleling the iron reduction and the decrease of oxidative stress, a benefit was observed on glucose tolerance [58].

There are also indications that ferritin may have other functions in addition to its well-described role in storing intracellular iron, and in particular that it may act as a proxidant under some conditions leading to uncontrolled iron release. It has also been postulated that Cr^{3+} competes with Fe^{3+} for Tf binding [59]. Therefore, a high iron level might exclude chromium from binding to transferrin. This might participate in glucose impairment since chromium seems to have beneficial effects in glucose tolerance [60]. Iron also interacts with Zn, which acts as an antioxidant in protecting protein from iron damage, in multiple ways, and Zn is also necessary for insulin secretion and diabetes prevention [61].

Both localized and generalized iron excess, as well as deficiency, are situations in which free radical damage has been observed with functional disturbance including genetic alterations [8]. It is worth noting that mild dietary iron overload did not lead to any significant increase in lipid peroxidation followed by TBARS content, probably because the iron content after iron supplementation was underestimated in plasma as compared to liver [62]. Nevertheless a positive correlation between iron level and lipid peroxidation has been described in non-iron supplemented pregnant women [63], confirming the relationship between oxidative stress and iron status.

During pregnancy, despite increased defence mechanisms, increased oxidative stress occurs as compared to non-pregnant women [28], and this oxidative imbalance is further increased in the case of GDM. It is well-documented that hyperglycaemia induces OS through several metabolic mechanisms, including the polyol pathway, formation of advanced glycation end products, activation of protein kinase C, the hexosamine pathway and increased OS generation by enhanced reactive oxygen species production by mitochondria [64]. Elevated OS was associated with GDM in several studies which demonstrated impaired antioxidant enzymes and total antioxidant status with elevated markers of lipid peroxidation, protein oxidation at the time of diagnosis for GDM (24–28 weeks of gestation) or at delivery [28]. An association between oxidative DNA damage assessed in early pregnancy before 20 weeks of gestation and risk for GDM has also been reported [65]. We have also confirmed the same effect [66].

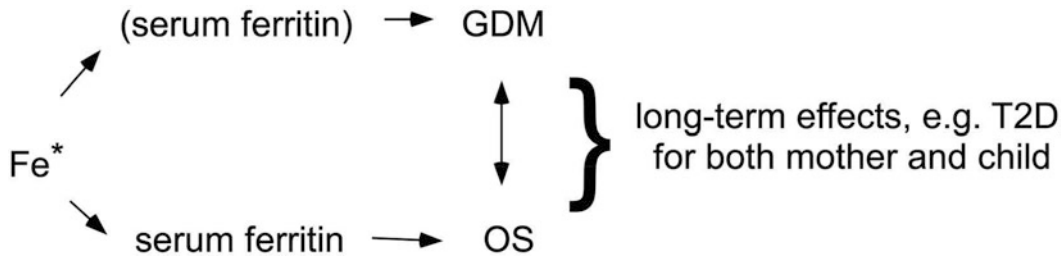


Fig. 36.1 Deregulated iron (Fe^{*}) as a key factor of GDM and OS in pregnancy

Some epidemiological studies examining the association of iron supplementation in pregnancy and subsequent elevated OS are available. The effect of a daily combined iron supplementation (100 mg as fumarate) increased the plasma levels of lipid peroxidation in two studies [67, 68]. The iron supplementation scheme might play a role in the effect on lipid peroxidation, since a daily supplementation has been shown to increase it significantly near term, whereas weekly supplementation decreased it [69], supporting that sustained iron accumulation is a factor of oxidative stress.

Links relating iron status, OS and GDM are summarized in Fig. 36.1.

Regarding iron and offspring, recent experimental evidence suggests that, whereas body iron homeostasis is tightly regulated and is still sensitive to dietary iron intake, early life iron overload in mice has significant effects on neurobehavioral performance and neonatal iron supplementation alters brain iron levels in adult animals resulting in neurodegeneration with age [70]. In an experimental model of gestational diabetes associated with high iron intake but within the normal range, we reported that, despite the apparently similar OS level among the mothers fed with the Fructose-diet and the Fructose-Iron one, a significant difference in the redox status of the livers and brains of newborns was detected: this suggests that foetuses were more sensitive to the proxidant effect of iron during pregnancy than their mothers [71].

The link between high iron and oxidative stress deserves further investigation to evaluate the consequences not only based on the mothers' plasma markers but also on offspring throughout life.

Recommendations

Since the clinical consequences of suspected iron deficiency without anaemia, assessed by a low ferritin concentration but with normal haemoglobin values, are unknown, iron supplementation should be avoided in women at high risk of GDM after excluding nutritional anaemia.

In women with a high risk of GDM, ferritin level above 40 µg/L early in pregnancy should be considered as a risk factor of favoured glucose impairment and of oxidative stress.

Women with high risk of GDM and without anaemia should avoid high intake of haem iron before and at early pregnancy.

In women at risk of GDM, glycemia, haemoglobin and ferritin measurements should be proposed very early in pregnancy or at the initial prenatal visit, to benefit from specific dietary advice in case of high haemoglobin and ferritin status even within the normal range.

A proposal for a decision tree relative to the iron status is illustrated in Fig. 36.2.

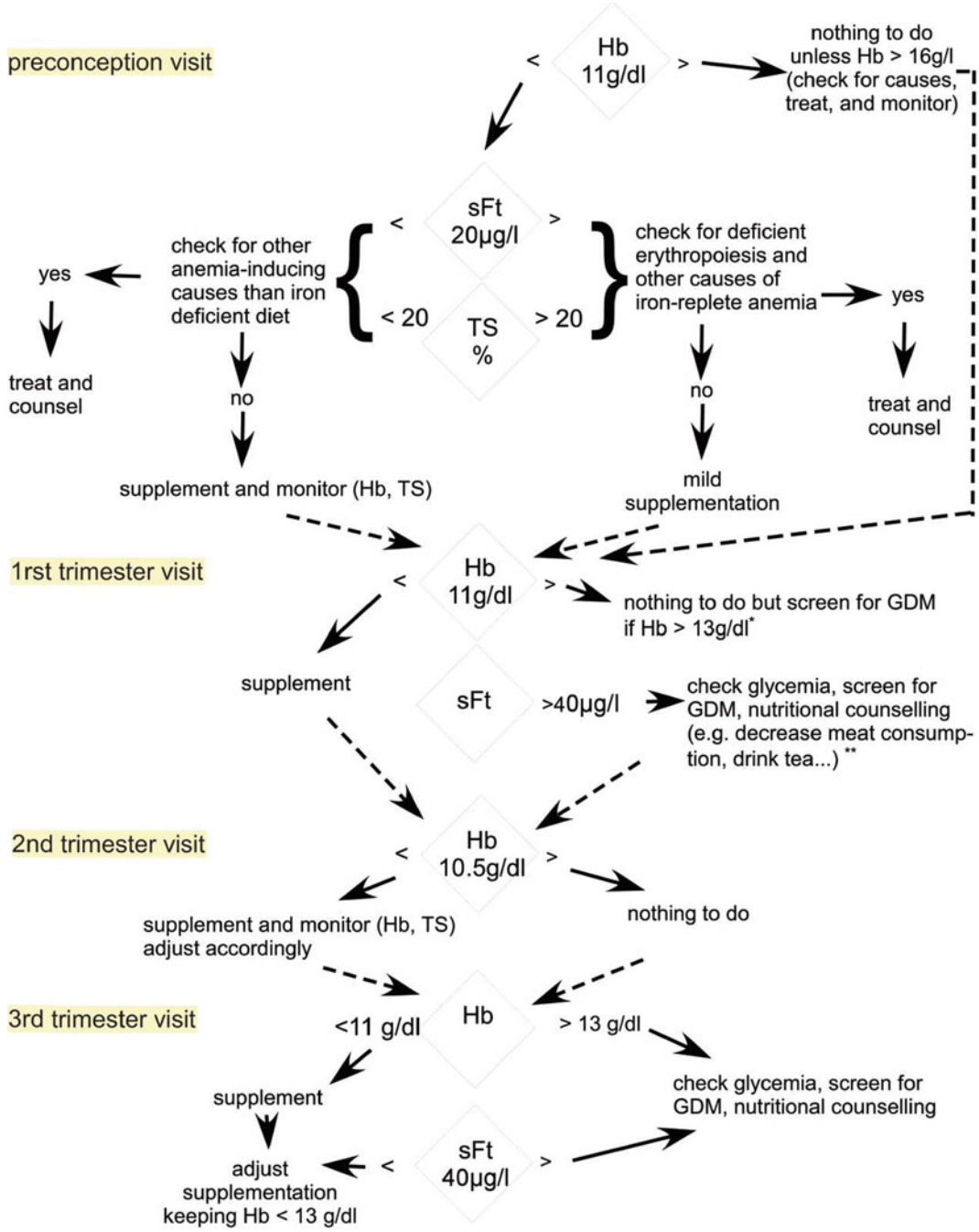


Fig. 36.2 Schematic decision tree for iron supplementation during pregnancy. Often the information gathered before and during the first trimester will have to be obtained at the first visit. sFt: serum ferritin; Hb haemoglobin; TS: transferrin saturation. *cases of pathological high Hb concentrations include polycythemia, and most relevant to pregnancy, impaired increase of plasma volume (hypovolemia) smoking with ineffective CO-inhibited Hb, and preeclampsia. **in most advanced overload cases, iron chelation might be considered although, to our knowledge, this has never been recommended during pregnancy for non-pathologically overloaded subjects by any authoritative body

Conclusion

Since GDM accounts for one of the most important disease during pregnancy, risk factors have important clinical and public health connotations, and biological and dietary advice including food iron intake should be provided to modulate glucose intolerance

Accumulating evidence suggests association between a high level of haemoglobin >13 g/dL and poor outcomes during pregnancy. Since pregnancy is a critical period for short- and long-term increased risk of glucose intolerance and Type 2 diabetes both in mothers and newborn, it is worth focusing on haemoglobin as the "gold standard" of iron homeostasis during pregnancy (Fig. 36.2). Increased moderate ferritin concentrations (e.g. level >40 μg/l) at early pregnancy should be used as a biological marker of GDM risk, but low values should not compulsorily justify iron supplementation (Fig. 36.2) unless they fall well below the physiological range, e.g. 20 μg/l, which might be lower in pregnancy (no data are yet available). Recent studies showing that haem iron in the preconceptional period is a possible risk factor of GDM, call for a need for dietary counselling and it should be provided to all women at risk of GDM, in particular those displaying high ferritin values in blood. In the future, ongoing advances in the understanding of iron homeostasis may define new options for screening tests like assays of hepcidin in addition to more conventional ones such as transferrin and its saturation. These measurements may prove useful in predicting the response to absorption of oral iron in iron deficiency. More mechanistic studies are warranted to probe the ideas presented herein, since it is becoming increasingly evident that high haem-Fe is related to the incidence of GDM, whereas non-haem and supplemental iron in the pre-conceptional period, but not at mid-pregnancy, might have beneficial effects.

Lastly, further experimental studies are also necessary to evaluate the epigenetic impact of iron intake and oxidative stress during pregnancy and the risk of chronic diseases such as Type 2 diabetes and neurodegenerative diseases later in life for neonates.

Note Due to space limitations all relevant original literature could not be quoted, and we apologize to scientists whose work has not been cited.

References

1. Rani PR, Begum J. Screening and diagnosis of gestational diabetes mellitus, where do we stand. J Clin Diagn Res. 2016;10(4):QE01–4.
2. Kennelly MA, McAuliffe FM. Prediction and prevention of gestational diabetes: an update of recent literature. Eur J Obstet Gynecol Reprod Biol. 2016;202:92–8.
3. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36(Suppl 1):S67–74.
4. Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? Diabetes Care. 2007;30(Suppl 2):S105–11.
5. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. Diabetologia. 2016;59(7):1396–9.
6. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D'Agostino RB Jr, Liese AD, Vehik KS, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH case-control study. Diabetes Care. 2008;31(7):1422–6.
7. Weinberg ED. Are iron supplements appropriate for iron replete pregnant women? Med Hypotheses. 2009;73(5):714–5.
8. Casanueva E, Viteri FE. Iron and oxidative stress in pregnancy. J Nutr. 2003;133(5 Suppl 2):1700S–8S.
9. CfDCa Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR Recomm Rep. 1998;7(4):1–29.
10. WHO. Assessing the iron status of populations: including literature reviews: report of a joint world health organization/centers for disease control and prevention technical consultation on the assessment of iron status at the

population level, Geneva, Switzerland, 6–8 2004 WHO document production services. Geneva: World Health Organization, 2004.
11. WHO. WHO: Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organisation: 2011.
12. WHO. Iron deficiency anemia assessment prevention and control: a guide for program managers. 2001.
13. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol. 2008;87(12):949–59.
14. McDonagh M, Cantor A, Bougatsos C, Dana T, Blazina I. Routine iron supplementation and screening for iron deficiency anemia in pregnant women: a systematic review to update the US preventive services task force recommendation. Rockville (MD)2015.
15. Galan P, Yoon HC, Preziosi P, Viteri F, Valeix P, Fieux B, et al. Determining factors in the iron status of adult women in the SU. VI. MAX study. Supplementation en VItamines et Mineraux AntioXydants. Eur J Clin Nutr. 1998;52(6):383–8.
16. Barrett JF, Whittaker PG, Williams JG, Lind T. Absorption of non-haem iron from food during normal pregnancy. BMJ. 1994;309(6947):79–82.
17. Bradley J, Leibold EA, Harris ZL, Wobken JD, Clarke S, Zumbrennen KB, et al. Influence of gestational age and fetal iron status on IRP activity and iron transporter protein expression in third-trimester human placenta. Am J Physiol Regul Integr Comp Physiol. 2004;287(4):R894–901.
18. Cheng Y, Zak O, Aisen P, Harrison SC, Walz T. Structure of the human transferrin receptor-transferrin complex. Cell. 2004;116(4):565–76.
19. Bastin J, Drakesmith H, Rees M, Sargent I, Townsend A. Localisation of proteins of iron metabolism in the human placenta and liver. Br J Haematol. 2006;134(5):532–43.
20. Collard KJ. Iron homeostasis in the neonate. Pediatrics. 2009;123(4):1208–16.
21. Fleming AF, Ghatoura GB, Harrison KA, Briggs ND, Dunn DT. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. Ann Trop Med Parasitol. 1986;80(2):211–33.
22. Milman N, Agger AO, Nielsen OJ. Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women. Dan Med Bull. 1991;38(6):471–6.
23. Byg KE, Milman N, Hansen S, Agger AO. Serum ferritin is a reliable, non-invasive test for iron status in pregnancy: comparison of ferritin with other iron status markers in a longitudinal study on healthy pregnant women. Erythropoiesis. Hematol. 2000;5(4):319–25.
24. De Benaze C, Galan P, Wainer R, Hercberg S. [Prevention of iron-deficiency anemia in pregnancy using early iron supplementation: a controlled trial]. Rev Epidemiol Sante Publique. 1989;37(2):109–18. Prevention de l'anemie ferriprive au cours de la grossesse par une supplementation martiale precoce: un essai controle.
25. Milman N, Byg KE, Agger AO. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. Acta Obstet Gynecol Scand. 2000;79(2):89–98.
26. Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. Am J Clin Nutr. 2003;78(4):773–81.
27. Pena-Rosas JP, De-Regal LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015(7):CD004736.
28. Zein S, Rachidi S, Hininger-Favier I. Is oxidative stress induced by iron status associated with gestational diabetes mellitus? J Trace Elem Med Biol. 2014;28(1):65–9.
29. Hansen JB, Moen IW, Mandrup-Poulsen T. Iron: the hard player in diabetes pathophysiology. Acta Physiol (Oxf). 2014;210(4):717–32.
30. Arija V, Fernandez-Cao JC, Basora J, Bullo M, Aranda N, Estruch R, et al. Excess body iron and the risk of type 2 diabetes mellitus: a nested case-control in the PREDIMED (PREvention with MEDiterranean Diet) study. Br J Nutr. 2014;112(11):1896–904.
31. Rajpathak SN, Wylie-Rosett J, Gunter MJ, Negassa A, Kabat GC, Rohan TE, et al. Biomarkers of body iron stores and risk of developing type 2 diabetes. Diabetes Obes Metab. 2009;11(5):472–9.
32. Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE, Hu FB. The role of iron in type 2 diabetes in humans. Biochim Biophys Acta. 2009;1790(7):671–81.
33. Abril-Ulloa V, Flores-Mateo G, Sola-Alberich R, Manuel-y-Keenoy B, Arija V. Ferritin levels and risk of metabolic syndrome: meta-analysis of observational studies. BMC Public Health. 2014;14:483.
34. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. Diabetes Care. 2004;27(9):2108–15.
35. Lao TT, Tam KF. Maternal serum ferritin and gestational impaired glucose tolerance. Diabetes Care. 1997;20 (9):1368–9.
36. Lao TT, Chan PL, Tam KF. Gestational diabetes mellitus in the last trimester—a feature of maternal iron excess? Diabet Med. 2001;18(3):218–23.
37. Tarim E, Kilicdag E, Bagis T, Ergin T. High maternal hemoglobin and ferritin values as risk factors for gestational diabetes. Int J Gynaecol Obstet. 2004;84(3):259–61.

38. Lao TT, Chan LY, Tam KF, Ho LF. Maternal hemoglobin and risk of gestational diabetes mellitus in Chinese women. Obstet Gynecol. 2002;99(5 Pt 1):807–12.
39. Lao TT, Ho LF. Impact of iron deficiency anemia on prevalence of gestational diabetes mellitus. Diabetes Care. 2004;27(3):650–6.
40. Zein S, Rachidi S, Awada S, Osman M, Al-Hajje A, Shami N, et al. High iron level in early pregnancy increased glucose intolerance. J Trace Elem Med Biol. 2015;30:220–5.
41. Khambalia AZ, Aimone A, Nagubandi P, Roberts CL, McElduff A, Morris JM, et al. High maternal iron status, dietary iron intake and iron supplement use in pregnancy and risk of gestational diabetes mellitus: a prospective study and systematic review. Diabet Med. 2015.
42. Fu S, Li F, Zhou J, Liu Z. The relationship between body iron status, iron intake and gestational diabetes: a systematic review and meta-analysis. Med (Baltimore). 2016;95(2):e2383.
43. Moyer VA. Force USPST. screening for gestational diabetes mellitus: U.S. preventive services task force recommendation statement. Ann Intern Med. 2014;160(6):414–20.
44. Chan KK, Chan BC, Lam KF, Tam S, Lao TT. Iron supplement in pregnancy and development of gestational diabetes–a randomised placebo-controlled trial. BJOG. 2009;116(6):789–97; discussion 97–8.
45. Bo S, Menato G, Villois P, Gambino R, Cassader M, Cotrino I, et al. Iron supplementation and gestational diabetes in midpregnancy. Am J Obstet Gynecol. 2009;201(2):158 ;e1–6.
46. Helin A, Kinnunen TI, Raitanen J, Ahonen S, Virtanen SM, Luoto R. Iron intake, haemoglobin and risk of gestational diabetes: a prospective cohort study. BMJ open. 2012;2(5).
47. Fernandez-Real JM, Lopez-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. Diabetes. 2002;51(8):2348–54.
48. Bowers K, Yeung E, Williams MA, Qi L, Tobias DK, Hu FB, et al. A prospective study of prepregnancy dietary iron intake and risk for gestational diabetes mellitus. Diabetes Care. 2011;34(7):1557–63.
49. Darling AM, Mitchell AA, Werler MM. Preconceptional iron intake and gestational diabetes mellitus. Int J Environ Res Public Health. 2016;13(6).
50. Buijsse B, Feskens EJ, Moschandreas J, Jansen EH, Jacobs DR Jr, Kafatos A, et al. Oxidative stress, and iron and antioxidant status in elderly men: differences between the Mediterranean south (Crete) and northern Europe (Zutphen). Eur J Cardiovasc Prev Rehabil. 2007;14(4):495–500.
51. Tobias DK, Zhang C, Chavarro J, Bowers K, Rich-Edwards J, Rosner B, et al. Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. Am J Clin Nutr. 2012;96(2):289–95.
52. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr. 2011;94(6 Suppl):1975S–9S.
53. Afkhami-Ardekani M, Rashidi M. Iron status in women with and without gestational diabetes mellitus. J Diabetes Complications. 2009;23(3):194–8.
54. Leonard SS, Harris GK, Shi X. Metal-induced oxidative stress and signal transduction. Free Radic Biol Med. 2004;37(12):1921–42.
55. Wei W, Liu Q, Tan Y, Liu L, Li X, Cai L. Oxidative stress, diabetes, and diabetic complications. Hemoglobin. 2009;33(5):370–7.
56. Whittaker P, Hines FA, Robl MG, Dunkel VC. Histopathological evaluation of liver, pancreas, spleen, and heart from iron-overloaded Sprague-Dawley rats. Toxicol Pathol. 1996;24(5):558–63.
57. Lenzen S. Oxidative stress: the vulnerable beta-cell. Biochem Soc Trans. 2008;36(Pt 3):343–7.
58. Kom GD, Schwedhelm E, Nielsen P, Boger RH. Increased urinary excretion of 8-iso-prostaglandin F2alpha in patients with HFE-related hemochromatosis: a case-control study. Free Radic Biol Med. 2006;40(7):1194–200.
59. Quarles CD Jr, Marcus RK, Brumaghim JL. Competitive binding of Fe3+, Cr3+, and Ni2+ to transferrin. J Biol Inorg Chem. 2011;16(6):913–21.
60. Vincent JB. Is the pharmacological mode of action of chromium(III) as a second messenger? Biol Trace Elem Res. 2015;166(1):7–12.
61. Ranasinghe P, Pigera S, Galappatthy P, Katulanda P, Constantine GR. Zinc and diabetes mellitus: understanding molecular mechanisms and clinical implications. Daru. 2015;23:44.
62. Puntarulo S. Iron, oxidative stress and human health. Mol Aspects Med. 2005;26(4–5):299–312.
63. Hininger I, Favier M, Arnaud J, Faure H, Thoulon JM, Hariveau E, et al. Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. Eur J Clin Nutr. 2004;58(1):52–9.
64. Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal. 2011;15(12):3061–100.
65. Qiu C, Hevner K, Abetew D, Enquobahrie DA, Williams MA. Oxidative DNA damage in early pregnancy and risk of gestational diabetes mellitus: a pilot study. Clin Biochem. 2011;44(10–11):804–8.
66. Zein S, Rachidi S, Shami N, Sharara I, Cheikh-Ali K, Gauchez AS, Moulis JM, Ayoubi JM, Salameh P, Hininger-Favier. Association between iron level, glucose impairment and increased DNA damage during pregnancy. J Trace Elem Med Biol. 2016; doi:10.1016/j.jtemb.2016.11.006 [Epub ahead of print].

67. Lachili B, Hininger I, Faure H, Arnaud J, Richard MJ, Favier A, et al. Increased lipid peroxidation in pregnant women after iron and vitamin C supplementation. Biol Trace Elem Res. 2001;83(2):103–10.
68. Devrim E, Tarhan I, Erguder IB, Durak I. Oxidant/antioxidant status of placenta, blood, and cord blood samples from pregnant women supplemented with iron. J Soc Gynecol Investig. 2006;13(7):502–5.
69. Viteri FE, Casanueva E, Tolentino MC, Diaz-Frances J, Erazo AB. Antenatal iron supplements consumed daily produce oxidative stress in contrast to weekly supplementation in Mexican non-anemic women. Reprod Toxicol. 2012;34(1):125–32.
70. Berggren KL, Chen J, Fox J, Miller J, Dodds L, Dugas B, et al. Neonatal iron supplementation potentiates oxidative stress, energetic dysfunction and neurodegeneration in the R6/2 mouse model of Huntington's disease. Redox Biol. 2015;4:363–74.
71. Zein S, Sitti F, Osman M, Arnaud J, Batandier C, Gauchez AS, et al. Middle iron-enriched fructose diet on gestational diabetes risk and on oxidative stress in offspring rats. Biol Trace Elem Res. 2016.

Part X
Resources

Chapter 37
Recommended Resources on Maternal Diabetes

Rajkumar Rajendram, Vinood B. Patel and Victor R. Preedy

Key Points

- Up to 5% of all pregnancies are affected by maternal diabetes.
- Maternal diabetes includes pre-gestational (12.5%) and gestational diabetes (87.5%).
- Development in maternal diabetes is a constantly evolving field.
- There are a variety of regulatory bodies, journals, books, and websites that are relevant to an evidence-based approach to maternal diabetes.

Keywords Diabetes · Pregnancy · Evidence · Resources · Books · Journals · Regulatory bodies · Professional societies

Introduction

Around 700,000 women give birth in England and Wales alone each year [1, 2]. Up to 5% of these have maternal diabetes [1, 2]. Some of those with maternal diabetes have pre-existing diabetes (Type 1 diabetes 7.5%; Type 2 diabetes 5%) [1]. However, the vast majority (87.5%) have gestational diabetes [1]. Gestational diabetes usually develops during the second trimester and may or may not resolve after pregnancy. The prevalence of maternal diabetes is increasing at least in part because of result of higher rates of obesity in the general population and more pregnancies in older women [1, 2]. Prevalence rates, however, vary on geographical, time, diagnostic, and population group basis (for example see [3–6]).

The signs and symptoms of diabetes have been described since the beginning of time. For example, the Ebers Papyrus which records medical knowledge from 1500 BC reveals that the ancient Egyptians associated polyuria with fatal outcomes [7]. Maternal diabetes mellitus is associated with

R. Rajendram (✉) · V.R. Preedy
Department of Nutrition and Dietetics, Nutritional Sciences Division,
School of Biomedical and Health Sciences, King's College London,
Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK
e-mail: rajkumarrajendram@doctors.org.uk

V.R. Preedy
e-mail: vrpkcl@gmail.com; victor.preedy@kcl.ac.uk

V.B. Patel
Faculty of Science and Technology, Department of Biomedical Sciences,
University of Westminster, 115 New Cavendish Street, London W1W 6UW, UK
e-mail: v.b.patel@westminster.ac.uk; vinood.patel@yahoo.co.uk

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1_37

risks to the woman and high levels of glucose are teratogenic to the developing fetus [1, 2, 8]. Screening for maternal diabetes and tight control of blood glucose during pregnancy are therefore required.

However, a Cochrane review published in 2016 concluded that high quality scientific evidence was not yet available to guide the choice of the best blood glucose target range for the management of maternal diabetes [8]. Regardless, from the initial descriptions of polyuria to the development of insulin therapy; the diagnosis and treatment of maternal diabetes have become more and more complicated as the understanding of the disease has grown.

It is now nearly impossible even for experienced scientists and clinicians to remain up-to-date. For those new to the field it is difficult to know which of the myriad of available sources are reliable. To assist colleagues who are interested in understanding more about maternal diabetes we have therefore produced tables containing reliable, up-to-date resources in this chapter. The experts who assisted with the compilation of these tables of resources are acknowledged below.

Tables 37.1–37.4 list the most up-to-date information on the regulatory bodies, organizations and professional societies (Table 37.1), websites (Table 37.2), journals (Table 37.3) and books (Table 37.4) that are most relevant to an evidence-based study of maternal diabetes.

Table 37.1 Regulatory bodies, organizations and professional societies

Academy of nutrition and dietetics www.eatright.org
American association of clinical endocrinologists www.aace.com/publications/endocrine-practice
American congress of obstetricians and gynecologists (ACOG) www.acog.org
American Diabetes Associations www.diabetes.org
Asociación mexicana de diabetes amdiabetes.org
Australasian diabetes in pregnancy society (ADIPS) www.dips.org
Canadian society for exercise physiology www.csep.ca
Department of endocrinology and diabetes center of excellence, EUROCLINIC www.euroclinic.gr/en/department/diabetes-unit-athens
Diabetes Australia www.diabetesaustralia.com.au
Diabetes Canada www.diabetes.ca
Diabetes New Zealand www.diabetes.org.nz/about_diabetes/gestational_diabetes
Diabetes NSW www.diabetesnsw.com.au
Diabetes UK www.diabetes.org.uk
Diabetic pregnancy study group (DPSG) www.dpsghome.org

(continued)

Table 37.1 (continued)

Endocrine Society www.endocrine.org
European association for the study of diabetes (EASD) www.easd.org
Federación mexicana de diabetes www.fmdiabetes.org
Grupo español de diabetes y embarazo (GEDE) www.sego.es/organizacion/grupos?g=diabetes
Institute of medicine www.nationalacademies.org
International diabetes federation www.idf.org
Iranian ministry of health and medical education www.mohme.gov.ir
Medicines and healthcare products regulatory agency (MHRA) www.mhra.gov.uk
National institute for health and care excellence www.nice.org.uk
National institutes of health www.nlm.nih.gov
Sociedad española de diabetes www.sediabetes.org
Sports medicine australia www.sma.org.au
World health organization www.who.int

This table lists the regulatory bodies, organizations, and professional societies involved with various aspects of the metabolism, physiology, and healthcare of maternal diabetes

Table 37.2 Relevant internet resources

Adipose tissue: not just fat themedicalbiochemistrypage.org/adipose-tissue.php
American diabetes association clinical practice recommendations professional.diabetes.org/content/clinical-practice-recommendations%20
American Diabetes Association Gestational Diabetes Guidelines www.ndei.org/ADA-diabetes-management-guidelines-diabetes-in-pregnancy-GDM.aspx.html
Breastfeeding after gestational diabetes pregnancy care.diabetesjournals.org/content/30/supplement-2/S161
Breastfeeding and diabetes www.babycenter.com/o_breastfeeding-and-diabetes-8683.bc
Breastfeeding and diabetes: What's the connection? diabetesstopshere.org/2012/08/28/breastfeeding-and-diabetes-whats-the-connection
Breastfeeding and gestational diabetes, part one: benefits to mother and baby wellroundedmama.blogspot.com/2014/06/breastfeeding-and-gestational-diabetes-18.html
Breastfeeding and maternal diabetes kellymom.com/bf/concerns*mother/diabetes-maternal
Breastfeeding may help prevent type 2 diabetes after gestational diabetes www.nih.gov/news-events/nih-research-matters/breastfeeding-may-help-prevent-type-2-diabetes-after-gestation

(continued)

Table 37.2 (continued)

China knowledge resource integrated database (CNKI) http://oversea.cnki.net/kns55/default.aspx
Diabetes mellitus and pregnancy emedicine.medscape.com/article/127547-overview
Diabetes and breastfeeding
www.laleche.org.uk/diabetes-and-breastfeeding
Diabetes in pregnancy: NICE guidelines www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021
Evidence Analysis Library www.andeal.org
Guide to pregnancy with diabetes www.diabetesforecast.org/2010/aug/a-guide-to-pregnancy-with diabetes.html?referrer=https://www.google.co.th
Gestational diabetes and breastfeeding: A special relationship www.plus-size-pregnancy.org/gdbfing.htm
Gestational diabetes evidence-based nutrition practice guidelines andevidencelibrary.com/topic.cfm?cat=3719
Glycemic index foundation http://www.pregnancybirthbaby.org.au/partners/glycemic-index-foundation
Glycaemic index guide, university of sydney www.glycemicindex.com
Foodball—The food biomarker alliance
foodmetabolome.org/about
International diabetes federation guidelines www.idf.org/guidelines
Mayo clinic www.mayoclinic.org
Medscape www.medscape.com
National glycohemoglobin standardization program (NGSP) www.ngsp.org/interf.asp
National institutes of health: office of dietary supplements ods.od.nih.gov
Online mendelian inheritance in man www.omim.org
Pathway commons www.pathwaycommons.org
Pubmed www.ncbi.nlm.nih.gov/pubmed/
WebMD www.webmd.com

This table lists some internet resources on the metabolism, physiology, and healthcare of maternal diabetes. Some sites can be used search for material indirectly or directly related to maternal diabetes (for example Pubmed, Mayo Clinic, etc.). Other resources can be found with the sites listed in Table 37.1

Table 37.3 Journals covering maternal diabetes

Journal of maternal fetal and neonatal medicine
Plos One
American journal of obstetrics and gynecology
Diabetes care
Obstetrics and gynecology
BMC pregnancy and childbirth
Diabetic medicine
American journal of perinatology
Diabetes research and clinical practice
Diabetologia
BJOG an international journal of obstetrics and gynaecology
Journal of clinical endocrinology and metabolism
Archives of gynecology and obstetrics
Maternal and child health journal
Acta obstetricia et gynecologica scandinavica
European journal of obstetrics gynecology and reproductive biology
Diabetes
Gynecological Endocrinology
Current diabetes reports
Australian and new zealand journal of obstetrics and gynecology
Placenta
Journal of obstetrics and gynecology research
Best practice and research clinical obstetrics and gynecology
Diabetes technology and therapeutics
Journal of perinatology

This table lists the top 25 journals publishing original research and review articles related to maternal diabetes. The list was generated from SCOPUS (www.scopus.com) using general descriptors "maternal diabetes" and "gestational diabetes." The journals are listed in descending order of the total number of articles published in the past five years. Of course, different indexing terms or different databases will produce different lists so this is a general guide only

Table 37.4 Relevant books and other publications

L. Allen, a prentice, encyclopedia of human nutrition, 2nd edition, Elsevier Academic Press, UK, 2015
A.M. Coulston, C.J. Boushey, M.G. Perruzzi, Nutrition in the prevention and treatment of disease, 3rd edition, Elsevier Academic Press, UK, 2013
P. Gluckman, M. Hanson, C.Y. Seng, A. Bardsley, Nutrition and lifestyle for pregnancy and breastfeeding Oxford University Press, UK, 2014
M. Hod, L.G. Jovanovic, G.C. Di Renzo, A. De Leiva, O. Langer, Textbook of diabetes and pregnancy 3rd edition, CRC Press, USA, 2016
International Diabetes Federation (IDF), IDF Diabetes atlas, 7th edition, International Diabetes Federation, Belgium, 2015
O. Langer, The diabetes in pregnancy dilemma: Leading change with proven solutions, 2nd edition, People's Medical Publishing House, USA, 2015
C. López-Tinoco, M. Aguilar-Diosdado, Gestational diabetes and oxidative stress. Advances in medicine and biology, Nova Science Publishers, USA, 2012
L. Marks, S.W. Olds, The complete book of breastfeeding, 4th edition, Workman Publishing, USA, 2010
W. Miller, S. Rollnick, Motivational interviewing: Helping people change, 3rd edition, Guilford Press, USA, 2012
L.F. Pallardo, J.L. Bartha, L. Herranz, Diabetes y embarazo, Edika Med, Spain, 2015
V.R. Preedy, R.J. Hunter, Adipokines, CRC Press, USA, 2011
V. Seshiah, Contemporary topics in gestational diabetes, Jp Medical Pub, USA, 2015

This table lists books on the metabolism and physiology of maternal diabetes

Acknowledgements We would like to thank the following authors for contributing to the development of this resource.

Aguilar-Diosdado M, Ali H, Barquiel B, Beltcheva O, Boyadzhieva M, Brunetti A, Collins C, Coustan DR, de Seymour JV, Diamanti-Kandarakis E, Guariguata L, Guelfi K, Ilias I, Moghaddam-Banaem L, Ramos MP, Saucedo R, Shyam S, Xiao H, Youngwanichsetha S.

References

1. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline, 2014; NG3.
2. Inkster ME, Fahey TP, Donnan PT, Leese GP, Mires GJ, Murphy DJ. Poor glycated haemoglobin control and adverse pregnancy outcomes in Type 1 and Type 2 diabetes mellitus: systematic review of observational studies. BMC Pregnancy and Childbirth. 2006;6:30.
3. Erjavec K, Polji anin T, Matijevi R Impact of the implementation of new WHO diagnostic criteria for gestational diabetes mellitus on prevalence and perinatal outcomes: a population-based study. J Pregnancy. 2016;2016:2670912. doi:10.1155/2016/2670912. Epub 2016 Dec 21.
4. Anna V, Hidde van der Ploeg P, Cheung NW, Huxley RR, Bauman AE. Sociodemographic correlates of the increasing trend in prevalence of gestational diabetes mellitus in a large population of women between 1995 and 2005 Diabetes Care. 2008 Dec; 31(12): 22882293.
5. Pedersen ML, Olesen J, Jrgensen ME, Damm P. Gestational diabetes mellitus in Greenland: a national study of prevalence and testing efficacy. Int J Circumpolar Health. 2016; 75: 10.3402/ijch.v75.32167. Published online 2016 Aug 24.
6. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the united states, pregnancy risk assessment monitoring system (PRAMS), 20072010 Prev Chronic Dis. 2014; 11: E104. Published online 2014 Jun 19. doi:10.5888/pcd11.130415.
7. Guthrie DW, Humphreys SS. Diabetes urine testing: an historical perspective. Diabetes Educ. 1988;14:521–6.
8. Martis R, Brown J, Alsweiler J, Crawford T, Crowther C.A. Different intensities of glycaemic control for women with gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2016; 4: CD011624. doi:10.1002/14651858.CD011624.pub2.

Index

Note: Page numbers followed by *f* and *t* indicate figures and tables respectively

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,
Nutrition and Health, https://doi.org/10.1007/978-3-319-56440-1